CLINICAL SIGNIFICANCE OF E-SELECTIN AND CTGF IN DIABETIC NEPHROPATHY, THEIR RELATIONSHIP WITH HBA1C AND INFLUENCING FACTORS OF DIABETIC NEPHROPATHY

Lihui Wang[1, 2, #], Jinhua Huang[3, #], Xuelun Wu[2], Xinsheng Li[2], Hongxia Qian[2], Jincheng Zhang[2], Mei Zhu[1, *]
[1]Department of Endocrinology and Metabolism, Tianjin Medical University General Hospital, Tianjin300052, China - [2]Department 1 of Endocrinology and diabetes mellitus, Cangzhou Central hospital, Cangzhou061001, Hebei Province, China - [3]Department of Endocrinology, BeiJing Zhongguancun Hospital, Beijing100080, China
[#]*These authors contributed equally to this study as co-first author*

ABSTRACT

Objective: *This study aims to explore the clinical significance of E-selectin (E-S) and connective tissue growth factor (CTGF) in diabetic nephropathy (DN).*

Patients and methods*: A total of 127 patients with diabetes admitted to our hospital were selected as the research objects and analyzed prospectively. Among them, 61 patients combined with nephropathy were divided into a research group. The other 66 patients with simple diabetes were divided into a control group. The levels of E-S, CTGF and HbA1c in serum of patients between the two groups were compared.*

Results*: E-S, CTGF and HbA1c in the research group were significantly higher than those in the control group (p<0.001). Pearson correlation coefficient analysis showed that E-S, CTGF and HbA1c in the research group were positively correlated (p<0.001). ROC curve analysis showed that the combined detection of E-S and CTGF had good predictive value for the occurrence of DN in diabetic patients. Logistic regression analysis showed that fasting blood glucose, glomerular filtration rate, urinary albumin excretion rate, urea nitrogen, creatinine, E-S and CTGF were independent risk factors for DN in diabetic patients.*

Conclusions*: E-S and CTGF are significantly increased in DN patients, and are positively correlated with HbA1c, which is expected to be an early screening index for DN in the future.*

Keywords: *DN, E-S, CTGF, HbA1c, diagnosis, influencing factors.*

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Introduction

Diabetic nephropathy (DN) is glomerulosclerosis caused by abnormal glucose metabolism in diabetes and accompanied by excessive urine protein content, which is currently one of the most common and important complications of diabetic patients[1, 2].

According to relevant surveys, more than 366 million people worldwide have been threatened by diabetes, and the morbidity of DN is increasing year by year[3]. The pathogenesis of DN is still unclear, and the physiological abnormalities of the disease are usually caused by long-term poor blood sugar control[4]. The second is due to glomerular changes, including basement membrane thickening, silt diaphragm enlargement, increased number of glomerular mesangial cells, etc. With the development of the disease process, nephrosclerosis is eventually caused, and more serious cases develop into renal carcinoma due to untimely treatment[5, 6]. Therefore, early diagnosis and prevention of DN are of great significance to the prognosis of patients, which is also one of the hot research diseases in clinical practice for a long time. Lozano-Maneiro

et al[7] believe that renin-angiotensin-aldosterone system can block the occurrence of DN, while Hou et al[8] indicate that salvianolic acid A can prevent DN by inhibiting AGE-RAGE signaling pathway to improve glomerular endothelial function.

However, with the development of research, E-selectin (E-S) has gradually been found to play a crucial role in the regulation of immune system[9-11]. E-S is mainly expressed in activated endothelial cells and can mediate the initial adhesion between polymorphonuclear leukocytes and endothelial cells[12]. Some studies suggest that E-S is closely related to atherosclerosis[13].

Connective tissue growth factor (CTGF), a new cysteine-rich growth factor family, can promote cell proliferation, migration and differentiation[14]. Recently, it has been continuously proved to be closely related to the occurrence of fibrosis in multiple tissues and organs (heart, pancreas, kidney, lung, etc.)[15, 16].

Due to its remarkable mitogen and chemotaxis, it can induce fibroblast proliferation and secrete ECM, which has attracted more and more attention[17]. At present, there is still little research on the correlation between E-S and CTGF in DN, and it is still unknown whether E-S and CTGF have any influence on DN. Because the disease process of DN is closely related to glomerulus and cell activities, we speculate that E-S and CTGF may be abnormally expressed in DN. In order to verify our conjecture, this experiment aims to explore the significance of E-S and CTGF in DN patients and provide new reference basis for clinical diagnosis and treatment of DN in the future.

Materials and methods

General data

A total of 127 patients with diabetes admitted to our hospital were selected as the research objects for prospective analysis. Among them, 61 patients combined with nephropathy were divided into the research group. There were 48 males and 13 females who were 49-70 years old, with an average age of (56.8±8.1) years. Eleven patients were in glomerular hyperfiltration and renal hypertrophy stage (stage I), 9 patients were in normal albuminuria stage (stage II), 14 patients were in early diabetic nephropathy stage (stage III), 16 patients were in clinical diabetic nephropathy stage (stage IV), and 11 patients were in end-stage renal failure (stage V).

The other 66 patients were patients with simple diabetes and they were divided into the control group. There were 45 males and 21 females who were 49-72 years, with an average age of (57.4±8.6) years. This experiment has been approved by the Ethics Committee of our hospital. All the above research subjects have signed an informed consent.

Inclusion and exclusion criteria

Inclusion criteria:

• All patients met the diagnostic criteria for diabetes 18;

• The urinary protein excretion rate of patients in the research group was continuously more than 200μg/min and the urine protein was positive in routine examination;

• The nuclide dynamic renal glomerular filtration rate increased and the renal volume measured by B-ultrasound increased significantly;

• Patients were 20-75 years old;

• Patients had complete case data;

• An informed consent shall be signed by the patients themselves or their immediate family members;

• There was no history of antibiotic treatment within 6 months before admission.

Exclusion criteria:

• Patients combined with tumor, other cardiovascular and cerebrovascular diseases, liver and kidney diseases;

• Patients with organ failure and liver dysfunction;

• Patients with drug allergy;

• Patients with low treatment compliance for mental diseases;

• Patients with physical disabilities who were unable to take care of themselves and stayed a long time in bed;

• Patients transferred to hospital.

Methods

Altogether 5 mL of fasting venous blood before treatment was taken from the patient, and after being left at room temperature for 30 min and centrifuged for 10 min (4000 rpm/min), the upper serum was obtained and divided into two parts.

One part was used to detect E-S (Shanghai Tecan Trading Co., Ltd., BE59061) and CTGF (the kit was purchased from Shanghai Jingkang Bioengineering Co., Ltd., JK-(a)-5176) in serum by enzyme linked immunosorbent assay (ELISA).

The operation process was strictly carried out in sterile environment according to the kit instructions.

The other used a fully automatic biochemical analyzer (BECKMAN COULTER, AU5800) to detect glycosylated hemoglobin (HbA1c).

Observation indicators

Leading indicators

The leading indicators were as follows: the concentrations of E-S, CTGF and HbA1c in serum of patients in the two groups, and the correlation between E-S, CTGF and HbA1c.

Secondary indicators

The secondary indicators were as follows: the situation of E-S and CTGF in DN patients with different stages, and risk factors for diabetic nephropathy complications.

Statistical methods

The results of this experiment were analyzed by SPSS24.0 statistical software (Shanghai Yuchuang Network Technology Co., Ltd) and all graphical results were drawn by Graphpad8 (Shenzhen Qiruitian Software Technology Co., Ltd). The counting data such as gender of patients, smoking or not were expressed in the form of (rate). Chi-square test was used for comparison between groups. The measurement data such as E-S and CTGF concentrations were expressed in the form of (mean±standard deviation).

T test was used for inter-group comparison. Multiple groups were compared by repeated measurement analysis of variance and bonferroni back testing. The diagnostic value was analyzed by ROC curve. Pearson correlation coefficient was used for correlation analysis. Logistic regression analysis was used to analyze the risk factors. When $p<0.050$, the difference was statistically significant.

Results

Comparison of general data

Comparing the general data of patients in the two groups, it was found that there were no significant differences in age, BMI, blood, total cholesterol, low density lipoprotein, gender, place of residence, smoking, drinking, educational level and type of diabetes ($p>0.050$).

However, there were significant differences in glomerular filtration rate, urinary albumin excretion rate, creatinine, course of disease and exercise habits ($p<0.001$). More details were shown in Table 1.

	Research group (n=61)	Control group (n=66)	t or x^2	*p*
Age (years)			0.404	0.687
	56.8±8.1	57.4±8.6		
BMI (kg/cm^2)			0.361	0.719
	26.85±4.65	27.16±5.01		
Systolic pressure (mmHg)			0.564	0.574
	152.62±12.87	153.86±11.92		
Diastolic pressure (mmHg)			0.706	0.480
	96.24±8.67	95.16±8.50		
Fasting blood glucose (mmol/L)			6.866	<0.001
	19.62±2.16	16.52±2.85		
Glomerular filtration rate (mL/min)			9.485	<0.001
	152.63±26.85	117.62±12.85		
Urine albumin excretion rate (μg/min)			37.711	<0.001
	162.52±30.62	18.62±4.71		
Urea nitrogen (mmol/L)			24.420	<0.001
	18.62±4.52	4.56±1.16		
Creatinine (μmol/mL)			31.048	<0.001
	192.47±26.54	82.62±10.62		
Total cholesterol (mmol/L)			0.235	0.815
	4.50±1.14	4.45±1.25		
Low density lipoprotein (mmol/L)			0.289	0.773
	3.58±0.62	3.61±0.55		
Course of disease (years)			4.186	<0.001
	3.26±1.26	2.47±0.84		
Gender			1.785	0.182
Male	48 (78.69)	45 (68.18)		
Female	13 (21.31)	21 (31.82)		
Place of residence			0.476	0.490
Town	51 (83.61)	58 (87.88)		
Countryside	10 (16.39)	8 (12.12)		
Smoking			0.231	0.631
Yes	42 (68.85)	48 (72.73)		
No	19 (31.15)	18 (27.27)		
Drinking			0.024	0.876
Yes	38 (62.30)	42 (63.64)		
No	23 (37.70)	24 (36.36)		
Exercise habits			22.672	<0.001
Yes	2 (3.28)	25 (37.88)		
No	59 (96.72)	41 (62.12)		
Education level			0258	0.611
< high school	36 (59.02)	36 (54.55)		
High school or higher	25 (40.98)	30 (45.45)		
Type of diabetes			0.029	0.865
Type I	24 (39.34)	25 (37.88)		
Type II	37 (60.66)	41 (62.12)		

Table 1: Comparison of general data (n(%)).

Comparison between E-S and CTGF

E-S, CTGF and HbA1c in the research group were significantly higher than those in the control group (p<0.001). More details were shown in Figure 1.

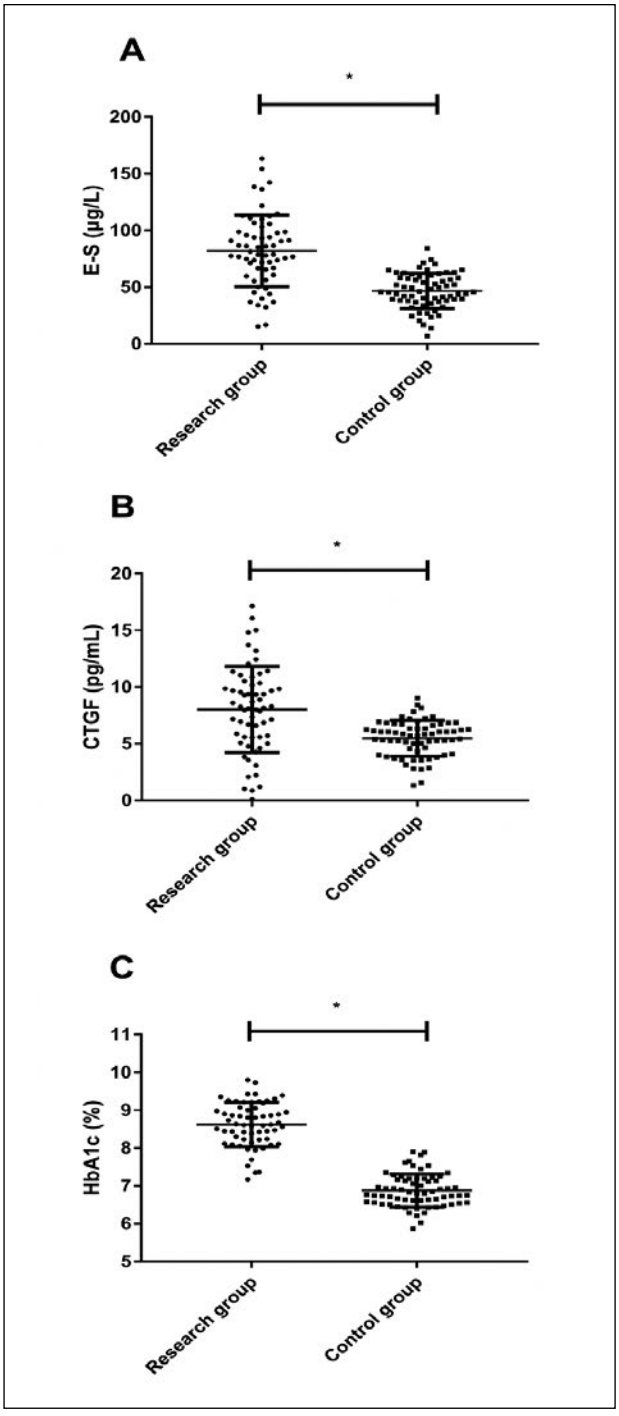

Figure 1: Comparison of E-S, CTGF and HbA1c of patients between the two groups.

*A) Compared with E-S of patients in two groups, E-S in the research group was significantly higher than that in the control group, *p<0.001. B) Compared with CTGF of patients in the two groups, CTGF in the research group was significantly higher than that in the control group, *p<0.001. C) Compared with HbA1c of patients in the two groups, HbA1c in the research group was significantly higher than that in the control group, *p<0.001.*

Diagnostic value of E-S and CTGF in DN

Results of ROC curve analysis showed that when cut-off value was 65.30, E-S had a predictive sensitivity of 75.41% and specificity of 92.42% for DN in diabetic patients. When cut-off value was 7.83, CTGF had a predictive sensitivity of 57.38% and specificity of 95.45% for DN in diabetic patients. Using E-S and CTGF as independent variables, binary Logistic regression analysis was carried out, and the prediction model Logit (P) =-7.017+0.074 E-S+0.383 CTGF was obtained. When cut-off value was 0.49, the prediction sensitivity and specificity of the modified model for diabetic DN were 80.33% and 89.39%, respectively. More details were shown in Table 2 and Figure 2.

	E-S	CTGF	E-S+CTGF
AUC	0.847	0.736	0.897
Std.Error	0.038	0.049	0.030
95%CI	0.774-0.921	0.641-0.831	0.839-0.955
p	<0.001	<0.001	<0.001
Cut-off	65.30	7.83	0.49
Sensitivity (%)	75.41	57.38	80.33
Specificity (%)	92.42	95.45	89.39
Youden index (%)	67.83	52.83	69.72

Table 2: Diagnostic value of E-S and CTGF for DN.

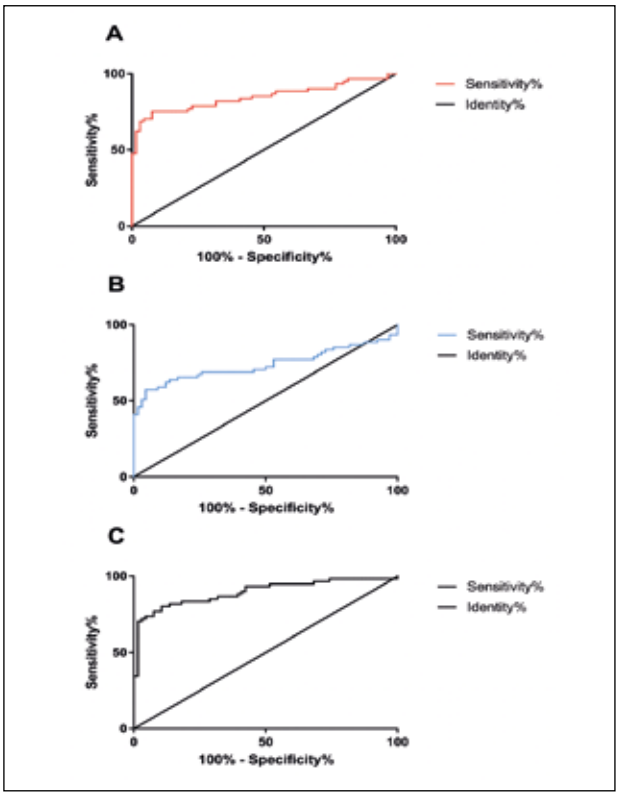

Figure 2: ROC curve analysis of E-S and CTGF for diabetic patients with DN.

A) ROC curve analysis of E-S for diabetic patients with DN B) ROC curve analysis of CTGF for diabetic patients with DN C) ROC curve analysis of combined detection of E-S and CTGF for diabetic patients with DN.

Correlation between E-S, CTGF and HbA1c

Pearson correlation coefficient analysis showed that E-S in the research group was positively correlated with HbA1c (r=0.716, p<0.001). CTGF was also positively correlated with HbA1c (r=0.567, p<0.001). More details were shown in Figure 3.

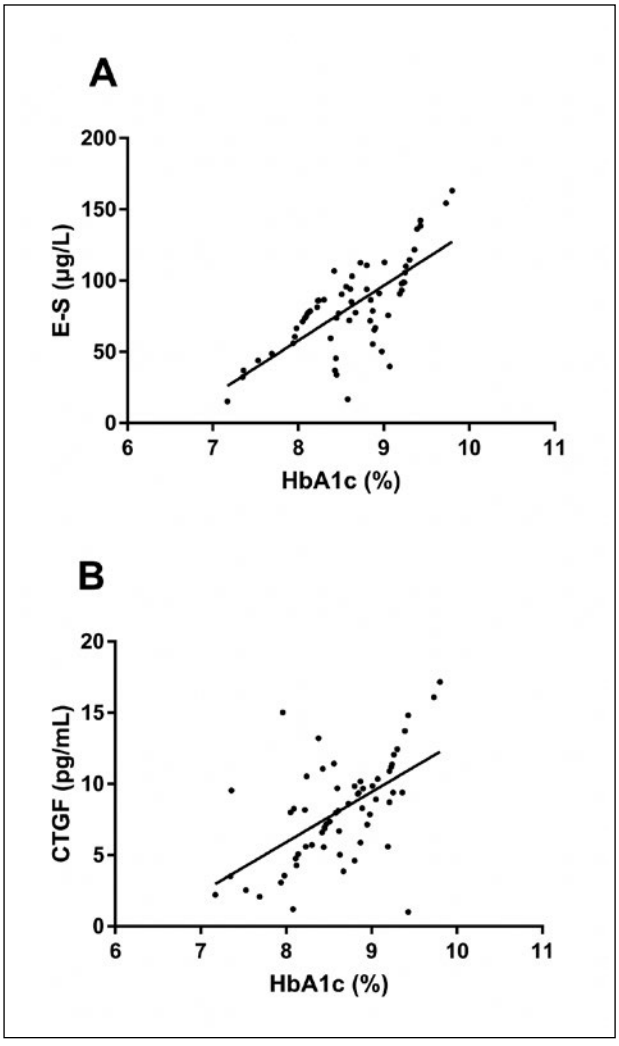

Figure 3: Correlation analysis of E-S, CTGF and HbA1c in the research.

A) Correlation analysis between E-S and HbA1c in the research group B) Correlation analysis of CTGF and HbA1c in the research group.

Comparison of E-S and CTGF in different stages of DN

Patients in stages I and II were divided into an early group (n=20), patients in stages III and IV were divided into a middle group (n=30), and patients in stage V were divided into a late group (n=11).

E-S and CTGF in the early group were significantly lower than those in the other two groups, while E-S and CTGF in the middle group were lower than those in the late group (p<0.001). More details were shown in Figure 4.

Comparison of E-S and CTGF in different stages of DN

Patients in stages I and II were divided into an early group (n=20), patients in stages III and IV were divided into a middle group (n=30), and patients in stage V were divided into a late group (n=11). E-S and CTGF in the early group were significantly lower than those in the other two groups, while E-S and CTGF in the middle group were lower than those in the late group (p<0.001). More details were shown in Figure 4.

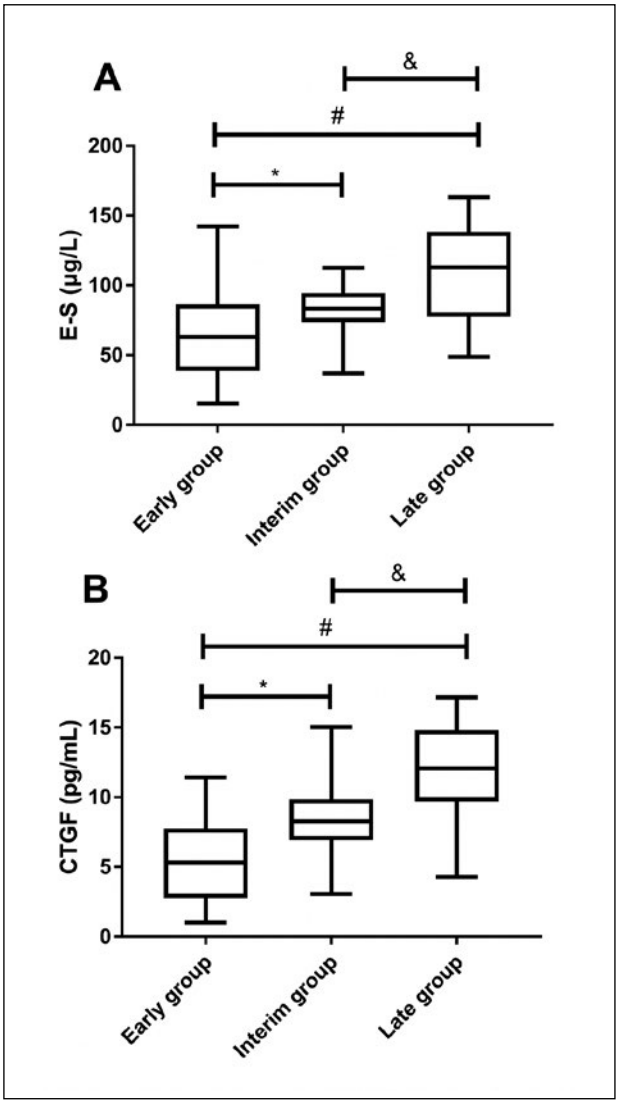

Figure 4: Comparison of E-S and CTGF in different stages of DN.

*A) Compared with E-S in different stages of DN, E-S in the early stage group was significantly lower than that in the middle stage group (*p<0.001) and the late stage group (#p<0.001), and E-S in the middle stage group was significantly lower than that in the late stage group (&p<0.001). B) Compared with CTGF in different stages of DN, CTGF in the early stage group was significantly lower than that in the middle stage group (*p<0.001) and the late stage group (#p<0.001), and CTGF in the middle stage group was significantly lower than that in the late stage group (&p<0.001).*

Analysis of risk factors affecting DN in diabetic patients

The indicators with differences in Table I and above were taken as single factor analysis results, and the indicators with differences were included for assignment (Table 3). Then we chose LR: Forward. Logistic regression analysis showed that the course of disease, exercise habits and HbA1c were not independent related factors that affected the occurrence of DN in diabetic patients (p>0.050), while fasting blood glucose (OR: 2.521), glomerular filtration rate (OR: 3.841), urinary albumin excretion rate (OR: 1.154), urea nitrogen (OR: 2.851), creatinine (OR: 4.541), E-S (OR: 3.522) and CTGF (OR: 4.652) were independent risk factors that affected the occurrence of DN in diabetic patients. More details were shown in Table 4.

Indicators	Assignment
Fasting blood glucose (mmol/L)	<19.62=0; ≥19.62=1
Glomerular filtration rate (mL/min)	<152.63=0; ≥152.63=1
Urinary albumin excretion rate (μg/min)	<162.52=0; ≥162.52=1
Urea nitrogen (mmol/L)	<18.62=0; ≥18.62=1
Creatinine (μmol/mL)	<192.47=0; ≥192.47=1
Course of disease (years)	<3.26=0; ≥3.26=1
Exercise habits	Yes = 0; None =1
E-S (μg/L)	<76.85=0; ≥76.85=1
CTGF (pg/mL)	<8.12=0; ≥8.12=1
HbA1c (%)	<8.66=0; ≥8.66=1

Table 3: Evaluation table (all measurement data took mean as the threshold value).

	B	Wald	S.E.	*p*	OR	95%CI
Fasting blood glucose	1.204	52.325	0.125	0.024	2.521	2.241-2.851
Glomerular filtration rate	2.212	62.521	0.032	0.000	3.841	3.412-4.521
Urinary albumin excretion rate	1.135	0.684	3.524	0.018	1.154	1.045-1.584
Urea nitrogen	2.106	89.256	0.068	0.000	2.851	2.842-2.956
Creatinine	4.526	112.62	0.036	0.000	4.541	3.262-7.562
E-S	3.452	78.621	0.019	0.000	3.522	2.162-4.682
CTGF	1.862	8.652	0.826	0.000	4.652	1.180-14.852

Table 4: Logistic regression analysis on DN of diabetic patients.

Discussion

DN is one of the most common microvascular diseases in diabetes. According to statistics, DN currently accounts for about 20.0%-40.0% of all diabetic patients[19]. The clinical symptoms are usually edema, hypertension, proteinuria and so on. However, in the process of disease development, the basic glomerular filtration rate of patients with early DN has not been seriously damaged. Conservative treatment can usually achieve certain results in clinical practice. However, once the disease progresses to the middle or late stage, renal function will usually suffer irreversible damage. At this time, only hemodialysis or kidney transplantation can achieve the therapeutic purpose[20, 21]. Therefore, finding an effective early screening index for DN is a hot and difficult point in clinical research. This study explores the influence of E-S and CTGF on DN and its clinical significance, which is of great clinical significance.

The experimental results show that E-S and CTGF are significantly increased in DN patients in the research group, suggesting that E-S and CTGF may be involved in the occurrence and development of DN. However, Qi and Gilbert's research results on E-S and CTGF in diabetes are consistent[22, 23], which can support the results of this experiment. E-S belongs to the selection family of adhesion molecules and mediates the initial adhesion of leukocytes to endothelial cells mainly by recognizing specific carbohydrate groups[24]. E-S consists of 589 amino acid residues and is located in chromosome 1 of human body. The level of E-S in serum can reflect the activation state of vascular endothelial cells[25]. DN is a diabetic microangiopathy, in which a significant increase in E-S can cause monocytes, neutrophils and the like in blood to adhere to vascular endothelium, and the expression and release of local growth factors increase, causing ischemia, hypoxia, thickening and other conditions of vascular basement[26]. According to some studies, advanced glycation end products (AGE) in DN can enhance the expression of selectin[27].

Therefore, we speculate that the disease process of E-S affecting DN may be that AGE modified circulating protein in blood activates other receptors to induce the expression of E-S on the surface of endothelial cells. At this time, combined with the effect of high glucose environment in the body of patients, the process of vascular injury and pathological changes is getting worse and worse, eventually leading to nephropathy. The increased expression of E-S mediates the adhesion between leukocytes and endothelial cells, causing microcirculatory disturbance[28], which can also be proved by our observation of the correlation between E-S and HbA1c. On the other hand, it also suggests that with the development of DN, the increase in the level of relevant cytokines also stimulates the

expression of E-S, forming a vicious circle and aggravating the condition of patients.

CTFG is a downstream signaling factor of TGF-β1 in promoting fibrosis activity, and it participates in TGF-β1-induced cell proliferation and extracellular matrix synthesis[29].

Some studies have claimed that the expression of CTFG in normal human serum is extremely low, and once kidney damage occurs, the expression will rapidly increase[30]. Duan et al[31] claim that CTFG can inhibit the interstitial transformation of bladder smooth muscle epithelial cells, and this effect is also applicable to renal tubular epithelial cells. Therefore, we believe that in DN patients, the renal tubular epithelial cells are stimulated by the high glucose environment of the body to cause the accelerated secretion of CTGF, promote the proliferation and hypertrophy of renal tubular epithelial cells, and accelerate the fibrosis process of renal interstitium. However, the positive correlation between CTGF and HbA1c also verifies the close relationship between CTGF and DN process, while Wu et al[32] believe that blocking the expression of CTGF may improve the renal protection, suggesting that CTGF may be a potential therapeutic target for DN in the future. However, because the experimental conditions are valid and cannot be verified, it is hoped that some researchers can carry out relevant experiments to confirm according to our conjecture.

However, through ROC curve analysis, we can see that when the cut-off value is 0.49, the prediction sensitivity and specificity of the modified model for diabetic DN are 80.33% and 89.39% respectively. It is suggested that E-S and CTGF can be used as early screening indicators for DN in the future to improve the early diagnosis rate of DN.

Logistic regression analysis shows that fasting blood glucose, glomerular filtration rate, urinary albumin excretion rate, urea nitrogen, creatinine, E-S and CTGF are independent risk factors for DN.

In future clinical diagnosis and treatment of DN patients, the following points should be paid attention to:

• Pay attention to the changes of blood glucose to avoid hypoglycemia caused by rapid hypoglycemia;

• Control diet, calculate food-related calories, and promote diversification of diet;

• Appropriate exercise: Appropriate exercise plans were customized according to the body condition of patients, in order to ensure that patients exercise at least 3-5 times a week;

• Psychological intervention: Patients should be taught of DN related knowledge and successful treatment cases so as to build their confidence to overcome the disease. However, glomerular filtration rate, urinary albumin excretion rate, urea nitrogen and creatinine as indicators of renal function have been studied a lot in the past, so they will not be repeated here.

This experiment is unable to know exactly the mechanism of action of E-S and CTGF on DN due to the failure to carry out basic experiments, and cannot judge the prognostic impact of E-S and CTGF on DN patients due to the short experimental period, which is our deficiency.

Discussion

E-S and CTGF are significantly increased in DN patients and are positively correlated with HbA1c, which is expected to be an early screening indicator for DN in the future.

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Corresponding Author:
Mei Zhu
Email: meichuqin@163.com
(China)