

THE DIAGNOSTIC VALUE OF SERUM TTCP-1, NUCB2 AND CXCL12 IN EARLY TYPE 2 DIABETIC NEPHROPATHY

DIJAGNOSTIČKA VREDNOST SERUMSKIH TTCP-1, NUCB2 I CXCL12 U RANOJ DIJABETIČKOJ NEFROPATIJU TIPA 2

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Summary

Background: To explore the combined diagnostic value of serum Tubuloin-1-Tyr carboxypeptidase 1 (TTCP-1), Nucleobindin-2 (NUCB2), and C-X-C Motif Chemokine Ligand 12 (CXCL12) for the early diagnosis of type 2 diabetic nephropathy (T2DN).

Methods: From May 2023 to May 2025, 184 patients with type 2 diabetes (T2DM) treated at this hospital comprised the T2DM group. These patients were further divided into a non-T2DN group (n=116) and a T2DN group (n=68) based on whether they developed T2DN. The control group consisted of 210 healthy people who had physicals at the same hospital during the same time period. An automated biochemical analyser was used to measure the levels of serum albumin and creatinine after fasting blood glucose (FBG), retinol binding protein (RBP), serum creatinine (Scr), uric acid (UA), blood urea nitrogen (BUN), and β 2-microglobulin (β 2-MG). The urine albumin-to-creatinine ratio (UACR) was calculated. The KD-EPI formula was used to estimate glomerular filtration rate (eGFR). The glycated haemoglobin level was detected using a glycated haemoglobin analyser. An automated chemiluminescent immunoassay measured fasting insulin levels, and the in-

Kratak sadržaj

Uvod: Cilj ove studije je bio da se ispita kombinovana dijagnostička vrednost serumskih tubuloin-1-tirozin karboksipeptidaze 1 (TTCP-1), nukleobindina-2 (NUCB2) i hemokina (C-X-C motiv) liganda 12 (CXCL12) u ranoj dijagnostici dijabetičke nefropatije tipa 2 (T2DN).

Metode: U periodu od maja 2023. do maja 2025. godine, 184 pacijenta sa dijabetes melitusom tipa 2 (T2DM) lečena u ovoj bolnici su činila grupu T2DM. Ovi pacijenti su dalje podeljeni na grupu bez T2DN (n=116) i grupu sa T2DN (n=68), u zavisnosti od toga da li je razvijena dijabetička nefropatija tipa 2. Kontrolnu grupu činilo je 210 zdravih osoba koje su u istom periodu obavile sistematski pregled u istoj bolnici. Automatski biohemijski analizator je korišćen za merenje nivoa albumina u serumu i kreatinina nakon određivanja glukoze natašte (FBG), proteina koji vezuje retinol (RBP), serumskog kreatinina (Scr), mokraćne kiseline (UA), azota ureje u krvi (BUN) i β 2-mikroglobulina (β 2-MG). Izračunat je odnos albumina i kreatinina u urinu (UACR). Procena glomerularne filtracije (eGFR) izvršena je primenom KD-EPI formule. Nivo glikozilovanog hemoglobina je određen analizatorom za glikozilirani hemoglobin. Nivo insulina natašte je meren hemiluminis-

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sulin resistance index (HOMA-IR) was calculated. The levels of TTCP-1, NUCB2, and CXCL12 were detected using enzyme-linked immunosorbent assays. Pearson correlation analysis was used to investigate the associations between TTCP-1, NUCB2, and CXCL12 levels and blood glucose and renal function indicators. Multivariate logistic regression analysis was employed to analyse the factors influencing T2DN occurrence. Receiver operating characteristic (ROC) curves were constructed to assess the diagnostic value of TTCP-1, NUCB2, and CXCL12 for T2DN.

Results: Compared with those in the control group, the levels of TTCP-1 and CXCL12 in the T2DM group increased, whereas NUCB2 levels dropped, and the variations were statistically significant ($P < 0.05$). In contrast to individuals in the non-T2DM group, those in the T2DM group had a longer duration of T2DM. The levels of FBG, HbA1c, HOMA-IR, RBP, UA, UACR, β 2-MG, BUN, Scr, TTCP-1, and CXCL12 were significantly lower. In comparison, eGFR and NUCB2 levels were significantly lower ($P < 0.05$). The levels of TTCP-1, NUCB2, and CXCL12 in the T2DM group were correlated with the duration of T2DM, FBG, HbA1c, HOMA-IR, RBP, UA, UACR, β 2-MG, BUN, Scr, and eGFR ($P < 0.05$). TTCP-1, NUCB2, and CXCL12 levels were independent influencing factors for the occurrence of T2DN ($P < 0.05$). The area under the curve for the combined diagnosis of T2DN by TTCP-1, NUCB2, and CXCL12 was 0.954, which was greater than that for the individual diagnoses ($Z(\text{combined} - \text{TTCP-1}) = 3.301$; $Z(\text{combined} - \text{NUCB2}) = 3.590$; $Z(\text{combined} - \text{CXCL12}) = 4.462$; all $P < 0.05$).

Conclusion: The levels of TTCP-1 and NUCB2 were elevated in T2DN patients, whereas the level of CXCL12 was decreased. These three factors are related to renal function indicators and blood sugar indicators. The combined diagnosis of these three factors could provide a theoretical basis for early clinical diagnosis and treatment.

Keywords: type 2 diabetic nephropathy, tubuliny-Tyr carboxypeptidase 1, nucleobindin-2, C-X-C motif chemokine ligand 12

Introduction

Type 2 diabetes (T2DM) is a multifactorial metabolic disorder, and its prevalence is increasing globally. Reduced insulin synthesis and secretion, insulin resistance, inflammation, and apoptosis are only a few of the pathological and physiological processes that contribute to the development, progression, and aggravation of disease (1). Usually associated with type 2 diabetes mellitus (T2DM), type 2 diabetic nephropathy (T2DN) is the main cause of end-stage renal disease and chronic kidney disease. Importantly, as the incidence of T2DM increases, the incidence of T2DN also increases (2). Therefore, analysing the factors related to the occurrence of T2DN can aid in the effective implementation of intervention measures, reduce its incidence, and improve quality of life.

Vascular endothelial cells and the target protein, vascular endothelial growth factor (VEGF), collaborate to produce tubuliny-Tyr carboxypepti-

centnim imunološkim testom, i izračunat je i indeks insulinske rezistencije (HOMA-IR). Nivoi TTCP-1, NUCB2 i CXCL12 određeni su enzimskim imunotestom (ELISA). Pearsonova korelaciona analiza je korišćena za ispitivanje povezanosti između nivoa TTCP-1, NUCB2 i CXCL12 i parametara glikoregulacije i bubrežne funkcije. Multivarijantna logistička regresiona analiza primenjena je za identifikaciju faktora koji utiču na pojavu T2DN. Za procenu dijagnostičke vrednosti TTCP-1, NUCB2 i CXCL12 u T2DN su korišćene ROC krive.

Rezultati: U poređenju sa kontrolnom grupom, nivoi TTCP-1 i CXCL12 su bili povišeni, dok je nivo NUCB2 bio snižen u T2DM grupi, a razlike su bile statistički značajne ($P < 0.05$). U poređenju sa pacijentima bez T2DN, pacijenti sa T2DN imali su duže trajanje dijabetesa tipa 2, kao i više vrednosti FBG, HbA1c, HOMA-IR, RBP, UA, UACR, β 2-MG, BUN i Scr, kao i viši nivo TTCP-1 i CXCL12, dok su eGFR i NUCB2 bili niži ($P < 0.05$). Nivoi TTCP-1, NUCB2 i CXCL12 bili su u korelaciji sa trajanjem T2DM, FBG, HbA1c, HOMA-IR i parametrima bubrežne funkcije ($P < 0.05$). Ovi markeri su predstavljali nezavisne faktore koji utiču na pojavu T2DN ($P < 0.05$). Površina ispod ROC krive za kombinovanu dijagnostiku T2DN pomoću TTCP-1, NUCB2 i CXCL12 iznosila je 0,954, što je bilo više nego kod pojedinačnih markera ($Z(\text{kombinovano} - \text{TTCP-1}) = 3,301$; $Z(\text{kombinovano} - \text{NUCB2}) = 3,590$; $Z(\text{kombinovano} - \text{CXCL12}) = 4,462$; svi $P < 0,05$).

Zaključak: Nivoi TTCP-1 i CXCL12 su bili povišeni kod pacijenata sa T2DN, dok je nivo NUCB2 bio snižen. Ova tri faktora su povezana sa parametrima bubrežne funkcije i regulacije glikemije. Njihova kombinovana primena može pružiti teorijsku osnovu za ranu kliničku dijagnostiku i lečenje.

Ključne reči: dijabetička nefropatija tipa 2, tubuliny-tirozin karboksipeptidaza 1, nukleobindin-2, hemokin (C-X-C motiv) ligand 12

dase 1 (TTCP-1), a newly discovered antiangiogenic agent. According to studies, TTCP-1 is also found in glomerular mesangial cells and may contribute to renal disorders through negative feedback (3). Nucleobindin-2 (NUCB2) is an anorectic neuropeptide widely expressed in the central nervous system and peripheral tissues, playing a role in the control of food consumption and lipid metabolism, as well as in the progression of metabolic-related diseases (4). In high-glucose- and hydrogen peroxide-induced renal epithelial cells, NUCB2 expression decreases, and its overexpression weakens cellular oxidative stress, apoptosis, and fibrosis, thereby protecting renal epithelial cells (5). C-X-C Motif Chemokine Ligand 12 (CXCL12) is a homeostatic CXC chemokine that binds to its receptor, CXC chemokine receptor 4 (CXCR4), and plays a crucial role in various pathological and physiological processes, such as embryogenesis, wound healing, angiogenesis, and tumour growth and proliferation (6). CXCL12 is expressed in various organs, including the kidneys,

and during kidney development, it contributes significantly to the formation of the renal vascular system through its interaction with CXCR4. Moreover, the CXCL12/CXCR4 axis plays important regulatory roles in the occurrence and development of diabetic nephropathy and chronic allograft nephropathy after kidney transplantation (7).

Therefore, this study aimed to investigate the early diagnostic value of the TTCP-1, NUCB2 and CXCL12 factors, which are related to kidney diseases, for T2DN by measuring their levels.

Materials and Methods

General information

A total of 184 T2DM patients, with an average age of 59.28 ± 8.50 years, were treated at our hospital between May 2023 and May 2025. Of these, 86 were male, and 98 were female. The control group consisted of 210 healthy individuals with an average age of 57.67 ± 7.15 years who underwent physical examinations at our hospital during the same time period. Of them, 112 were men, and 98 were women. When T2DM patients developed T2DN, they were divided into two groups: those with T2DN ($n=68$) and those without ($n=116$). The non-T2DN group consisted of 66 females and 50 males, with an average age of 58.77 ± 7.65 years and a duration of T2DM of 5.67 ± 1.50 years. The T2DN group comprised 32 females and 36 males, with an average age of 60.15 ± 9.46 years and a duration of T2DM of 7.22 ± 2.26 years.

Inclusion criteria

(1) The T2DM group met the following diagnostic criteria (8): A fasting blood glucose (FBG) level ≥ 7.0 mmol/L; a glycosylated haemoglobin (HbA1c) level $\geq 6.5\%$; a 2-hour blood glucose level ≥ 11.1 mmol/L following the oral glucose tolerance test (OGTT), fulfilling any of the aforementioned criteria; and the manifestation of characteristic symptoms of diabetes, including polydipsia, polyuria, and weight loss; (2) a T2DN group that met the following diagnostic criteria (9): a urine albumin-to-creatinine ratio (UACR) in the range of 30–300 mg/g; an estimated glomerular filtration rate (eGFR) < 60 mL/(min $\cdot$ 1.73 m ^{2}); and a diagnosis by renal biopsy; and (3) complete general information.

Exclusion criteria

(1) Infected patients; (2) patients with concurrent tumours; (3) patients who have undergone kidney transplantation or kidney dialysis; (4) patients with renal damage caused by other diseases; (5) patients who were treated with insulin before the

study; (6) patients with primary or secondary glomerular diseases; (7) patients with a rapid increase in eGFR in a short period of time and with "active" urinary sediment.

Testing method

Within 24 hours of admission for the patients (for the control group, on the day of the physical examination), 5 mL of peripheral venous blood was collected in a fasting state. The supernatant was obtained after low-temperature centrifugation and stored at -80°C until analysis. An automatic biochemical analyser (Rudu Life Sciences, Chemray 800) was used to measure FBG, retinol binding protein (RBP), serum creatinine (Scr), uric acid (UA), blood urea nitrogen (BUN), β 2-microglobulin (β 2-MG), and the levels of albumin and creatinine in urine and to calculate the UACR. Using the KD-EPI formula, eGFR was calculated. A glycosylated haemoglobin analyser (Hu Zhong Biology, MQ-6000) was used to detect the HbA1c level, and an automatic chemiluminescence immunoassay analyser (Roche, Cobas) was used to detect fasting insulin levels. The insulin resistance index (HOMA-IR) was calculated as follows: (fasting insulin $\times$ FBG)/22.5. Enzyme-linked immunosorbent assays were used to quantify TTCP-1 (Thermo Fisher, EH480RB), NUCB2 (Elirayt, E-EL-H2373), and CXCL12 (Celophy, S11671).

Statistical analysis

Data processing and analysis were conducted using SPSS 25.0 software. Data adhering to a normal distribution are represented as $\bar{x} \pm s$. For intergroup comparisons, t tests are used for continuous data, and χ^2 tests are used for categorical data presented as case numbers and percentages. Using Pearson correlation analysis, the associations between blood glucose and renal function markers and TTCP-1, NUCB2, and CXCL12 levels were examined. Multivariate logistic regression was used to analyse factors influencing T2DN occurrence. Receiver operating characteristic (ROC) curves were used to assess the diagnostic value of TTCP-1, NUCB2, and CXCL12 for T2DN, with differences in the area under the curve (AUC) compared using Z tests. A difference was considered to be statistically significant if $P < 0.05$.

Results

Comparison of serum TTCP-1, NUCB2, and CXCL12 levels between the control group and the T2DM group

There was no statistically significant difference in alcohol consumption or hyperlipidaemia between

Table I Comparison of serum TTCP-1, NUCB2, and CXCL12 levels between control group and T2DM group [n (%) or $\bar{x} \pm s$].

Item	Control group (n=210)	T2DM group (n=184)	T/ χ^2	P
Gender (Male)	112 (53.33)	86 (46.74)	0.856	0.359
Age (years)	57.67 $\pm$ 7.15	59.28 $\pm$ 8.50	1.443	0.155
BMI (kg/m ²)	22.17 $\pm$ 2.26	22.52 $\pm$ 2.31	1.362	0.175
Smoking	102 (48.57)	106 (57.61)	1.600	0.208
Drinking Wine	82 (39.05)	76 (41.30)	0.107	0.740
Merge underlying diseases				
Hypertension	94 (44.76)	86 (46.74)	0.070	0.784
Hyperlipidaemia	46 (21.90)	56 (30.43)	1.863	0.176
TTCP-1 (ng/L)	215.30 $\pm$ 65.41	476.23 $\pm$ 146.76	16.449	<0.001
NUCB2 (ng/L)	2.79 $\pm$ 0.76	1.52 $\pm$ 0.41	13.093	<0.001
CXCL12 (ng/mL)	1.80 $\pm$ 0.44	4.58 $\pm$ 1.40	13.081	<0.001

Table II General data comparison between non-T2DN group and T2DN group [n (%) or $\bar{x} \pm s$].

Item	Non T2DN group (n=116)	T2DN group (n=68)	T/ χ^2	P
Gender (Male)	50 (43.10)	36 (52.94)	0.836	0.364
Age (years)	58.77 $\pm$ 7.65	60.15 $\pm$ 9.46	0.760	0.448
BMI (kg/m ²)	22.76 $\pm$ 2.28	22.38 $\pm$ 2.39	0.761	0.448
Smoking	64 (55.17)	42 (61.76)	0.384	0.530
Drinking Wine	46 (39.66)	30 (44.12)	0.179	0.678
Merge underlying diseases				
Hypertension	52 (44.83)	34 (50.00)	0.233	0.634
Hyperlipidaemia	30 (25.86)	26 (38.24)	1.553	0.216
Duration of T2DM (years)	5.67 $\pm$ 1.50	7.22 $\pm$ 2.26	4.155	<0.001
Blood glucose indicators				
FBG (mmol/L)	6.57 $\pm$ 1.95	7.86 $\pm$ 2.57	2.758	0.001
HbA1c (%)	7.31 $\pm$ 1.88	8.60 $\pm$ 2.17	3.048	0.003
HOMA-IR	4.39 $\pm$ 1.21	6.20 $\pm$ 1.57	6.406	<0.001
Renal function indicators				
RBP (mg/L)	58.40 $\pm$ 17.35	73.59 $\pm$ 22.18	3.636	<0.001
UA (μ mol/L)	314.65 $\pm$ 72.46	438.20 $\pm$ 83.57	7.468	<0.001
UACR (mg/g)	24.31 $\pm$ 5.37	83.20 $\pm$ 23.78	18.184	<0.001
β 2-MG (mg/L)	3.50 $\pm$ 0.87	4.21 $\pm$ 1.10	3.378	0.001
BUN (mmol/L)	6.27 $\pm$ 1.61	8.29 $\pm$ 2.40	4.665	<0.001
Scr (μ mol/L)	74.18 $\pm$ 15.01	137.67 $\pm$ 25.84	14.910	<0.001
EGFR [mL/min $\cdot$ (1.73 m ²)]	107.46 $\pm$ 16.27	52.10 $\pm$ 7.51	18.657	<0.001
TTCP-1 (ng/L)	418.60 $\pm$ 121.86	574.38 $\pm$ 184.46	4.877	<0.001
NUCB2 (ng/L)	1.78 $\pm$ 0.55	1.35 $\pm$ 0.30	4.233	<0.001
CXCL12 (ng/mL)	3.89 $\pm$ 1.27	5.77 $\pm$ 1.80	5.798	<0.001

Table III Correlation analysis between TTCP-1, NUCB2, CXCL12 levels and blood glucose and renal function indicators in the T2DN group.

Item	TTCP-1	NUCB2	CXCL12			
	R	P	R	P	R	P
T2DM course	0.451	<0.001	-0.487	<0.001	0.427	<0.001
Blood glucose indicators						
FBG	0.475	<0.001	-0.468	<0.001	0.504	<0.001
HbA1c	0.468	<0.001	-0.536	<0.001	0.480	<0.001
HOMA-IR	0.461	<0.001	-0.537	<0.001	0.458	<0.001
Renal function indicators						
RBP	0.454	<0.001	-0.475	<0.001	0.512	<0.001
UA	0.466	<0.001	-0.489	<0.001	0.520	<0.001
UACR	0.451	≤0.001	-0.478	≤0.001	0.515	≤0.001
β2-MG	0.495	<0.001	-0.487	<0.001	0.471	≤0.001
BUN	0.469	<0.001	-0.584	<0.001	0.527	<0.001
Scr	0.452	<0.001	-0.559	<0.001	0.479	<0.001
EGFR	-0.486	<0.001	0.478	<0.001	-0.515	<0.001

the control group and the T2DM group ($P>0.05$); the serum levels of TTCP-1 and CXCL12 in the T2DM group were significantly greater than those in the control group, while the level of NUCB2 was significantly lower in the T2DM group than in the control group ($P<0.05$), see Table I.

Comparison of general data between the non-T2DN group and the T2DN group

There was no statistically significant difference in smoking or the presence of underlying diseases between the T2DN group and the non-T2DN group ($P>0.05$); the duration of T2DM in the T2DN group was longer than that in the non-T2DN group, and the blood glucose indicators (FBG, HbA1c, and HOMA-IR), renal function indicators (RBP, UA, UACR, β2-MG, BUN, and Scr), serum levels of TTCP-1 and CXCL12 were elevated in the T2DN group compared to the non-T2DN group, whereas the eGFR and NUCB2 level were lower in the T2DN group than in the non-T2DN group ($P<0.05$), see Table II.

Correlation analysis of the TTCP-1, NUCB2, and CXCL12 levels with blood glucose and renal function indicators in the T2DN group

In the T2DN group, the levels of TTCP-1 and CXCL12 were positively correlated with the duration of T2DM, blood glucose indicators (FBG, HbA1c,

and HOMA-IR), and renal function indicators (RBP, UA, UACR, β2-MG, BUN, and Scr) ($P<0.05$), whereas NUCB2 was negatively correlated with the duration of T2DM, blood glucose indicators (FBG, HbA1c, and HOMA-IR), and renal function indicators (RBP, UA, UACR, β2-MG, BUN, and Scr) ($P<0.05$). TTCP-1 and CXCL12 were negatively correlated with the eGFR. In contrast, NUCB2 showed a positive correlation with eGFR ($P<0.05$; see Table III).

Multivariate logistic regression investigation of the determinants affecting the incidence of T2DN

FBG, HbA1c, and HOMA-IR are indicators of blood glucose, whereas RBP, UA, UACR, β2-MG, BUN, and Scr are indicators of renal function. Therefore, only TTCP-1, NUCB2, CXCL12, HbA1c, and Scr were used as independent variables (all continuous variables, original values input), with T2DN occurrence (1 = occurred, 0 = not occurred) as the dependent variable in a multivariate logistic regression analysis. TTCP-1, NUCB2, and CXCL12 did not have multicollinearity with HbA1c or Scr. Elevated TTCP-1 and CXCL12 levels were independent risk factors for T2DN, and elevated NUCB2 levels were an independent protective factor ($P<0.05$; see Table IV).

Table IV Multivariate logistic regression analysis of influencing factors for T2DN occurrence.

Independent variable	β	SE	Wald χ^2	P	OR	95% CI	Collinearity	
							VIF	tolerance
TTCP-1	0.947	0.345	7.614	0.009	2.562	1.317~5.025	6.150	0.165
NUCB2	-0.552	0.217	6.817	0.002	0.575	0.379~0.873	4.238	0.239
CXCL12	0.739	0.284	6.687	0.002	2.081	1.207~3.625	3.476	0.281
HbA1c	0.223	0.128	3.099	0.071	1.249	0.978~1.595	5.199	0.195
Scr	0.626	0.374	2.825	0.096	1.868	0.904~3.852	2.130	0.461

Table V Diagnostic value of serum VASH1, NUCB2, and CXCL12 levels for the occurrence of T2DN.

Item	AUC	95%CI	P	Optimal critical value	Sensitivity (%)	Specificity (%)	Youden index
TTCP-1	0.810	0.726~0.893	<0.001	495.219 ng/L	76.40	75.89	0.526
NUCB2	0.804	0.708~0.870	<0.001	1.511 ng/L	73.56	70.62	0.445
CXCL12	0.730	0.638~0.827	<0.001	5.367 ng/mL	82.38	56.65	0.413
Joint diagnosis	0.954	0.888~0.988	<0.001	-	88.27	89.69	0.772

Diagnostic value of serum TTCP-1, NUCB2, and CXCL12 levels for the occurrence of T2DN

The area under the curve (AUC) values for diagnosing T2DN using TTCP-1, NUCB2, and CXCL12 alone were 0.810 (95% CI 0.726–0.893), 0.801 (95% CI 0.708–0.870), and 0.737 (95% CI 0.638–0.827), respectively. The AUC value for the combined diagnosis of the three was 0.954 (95% CI 0.888–0.988), which was superior to that for the individual diagnoses (Z for combined diagnosis - TTCP-1 = 3.301; Z for combined diagnosis - NUCB2=3.590; Z for combined diagnosis - CXCL12=4.462; all $P<0.05$), see Table V.

Discussion

Diabetes mellitus is a multisystem, chronic, noncommunicable disease. Obesity and a sedentary lifestyle are the causes of its rising prevalence worldwide. Numerous complications have a substantial impact on T2DM patients’ quality of life and place a heavy clinical and financial burden on the global community. End-stage renal disease is most frequently caused by T2DN, which is also one of the most prevalent microvascular consequences of T2DM. It raises the chance of negative outcomes and lowers the quality of life for patients (such as

cardiovascular events and mortality) (10). It is estimated that 35% to 40% of patients with T2DM will eventually develop T2DN. Metabolic abnormalities and genetics play significant roles in T2DN. Persistent hyperglycaemia leads to increased reactive oxygen species and advanced glycation end products, which, in turn, cause damage to large blood vessels and renal cells (11). In the early stage, T2DN patients present only with microalbuminuria. As the disease progresses, patients may develop massive proteinuria, oedema, hypertension, etc. In the advanced stage, they may develop renal failure, presenting with symptoms such as nausea and vomiting. They may require dialysis or kidney transplantation (12). Therefore, monitoring the progression of T2DN through serum markers can enable timely treatment and reduce renal damage.

TTCP-1 is a secreted protein that is produced mainly by endothelial cells and cells surrounding blood vessels. Under normal physiological conditions, it is expressed at low levels in various tissues, including vascular endothelial cells in organs such as the kidneys and liver, as well as in certain specific stromal cells. Additionally, its level changes during wound-healing and tissue-repair processes (13). Additionally, TTCP-1 is crucial in diabetic vascular disorders. Patients with diabetic retinopathy have higher serum levels of TTCP-1, a risk factor for retinal lesions and positively associated with blood sug-

ar and lipid levels, the duration of diabetes, and the severity of the disease (14). In patients with T2DN, serum levels of renal function indicators, inflammatory factors, and TTCP-1 increase, and TTCP-1 is associated with the degree of renal injury and the inflammatory response (15). In this investigation, the T2DM group's TTCP-1 score was higher than the control group's. Compared with the non-T2DN group, the T2DN group experienced T2DN for a longer period. Blood glucose indicators (FBG, HbA1c, and HOMA-IR), renal function indicators (RBP, UA, UACR, β 2-MG, BUN, and Scr), and serum TTCP-1 levels were higher in the T2DN group than in the non-T2DN group. The eGFR was lower in the T2DN group than in the non-T2DN group. Moreover, the TTCP-1 score was correlated with T2DM duration, blood glucose levels, and renal function indicators. These findings suggest that continuous exposure to high blood sugar may increase TTCP-1 secretion, thereby promoting angiogenesis and leading to renal damage.

NUCB2 is a cleavage product of the neuropeptide B/endorphin FQ receptor. Its sequence is highly conserved, and it is highly expressed in regulatory centres such as the hypothalamus and brainstem, where it participates in the central regulation of energy homeostasis. NUCB2 reduces energy intake by negatively regulating dopaminergic neuron activity, thereby reducing food intake (16). The NUCB2 level in T2DM patients was lower than in the control group. It was negatively correlated with the HOMA-IR score. It has high diagnostic accuracy for T2DM (17). In this study, NUCB2 levels were lower in the T2DM group than in the control group, and this was associated with T2DM duration, blood glucose indicators, and renal function indicators. An increase in its level is an independent protective factor against the occurrence of T2DM. These findings suggest that NUCB2 may exacerbate T2DM by regulating insulin sensitivity, leading to sustained hyperglycemia and subsequent kidney damage, and by promoting T2DM progression. The lower the NUCB2 level, the more severe the kidney damage.

CXCL12 is a small-molecule protein that is produced mainly by various cells, such as bone marrow stromal cells, endothelial cells, and fibroblasts. The production sites may vary across different tissues and organs. In the bone marrow, it is produced mainly by bone marrow stromal cells, whereas in the

liver and kidneys, it is produced mainly by endothelial cells and fibroblasts (18). Under hyperglycaemic conditions, these cells can stimulate CXCL12 secretion, leading to the accumulation of inflammatory cells in the kidneys, glomerular sclerosis, podocyte loss, and proteinuria. The level of CXCL12 in T2DN patients is significantly greater than that in patients with simple T2DM. It is an independent influencing factor for the occurrence of T2DN (19). T2DN patients not only have elevated CXCL12 levels but also show correlations with T2DM duration, blood glucose indicators, and renal function indicators. These findings suggest that hyperglycaemia in T2DM patients may increase CXCL12 levels, leading to the accumulation of inflammatory factors in the kidneys and a decline in renal function. CXCL12 is correlated with 24-hour urine protein excretion in T2DN patients and has relatively high predictive value for disease progression; thus, it can be used to assess the risk of disease progression after treatment (20–22). In this study, CXCL12 is useful for diagnosing T2DN, and when combined with TTCP-1 and NUCB2, the AUC and Youden index increase significantly, suggesting that the combined diagnosis of the three has greater clinical significance.

Conclusion

The levels of TTCP-1 and CXCL12 were elevated in T2DN patients, whereas NUCB2 levels were decreased. These three factors are independent influencing factors for the occurrence of T2DN. Combined diagnosis has greater clinical value than individual diagnosis does, providing effective diagnostic markers for early clinical condition assessment and prognosis evaluation. The shortcomings of this study include: only the levels of TTCP-1, NUCB2, and CXCL12 before treatment were measured; dynamic observation of the patient's condition changes during the process was lacking; and the changing trends of the three factors during disease progression were not understood. Further verification with a larger sample size is needed in the future.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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