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Expression of EZH2 and SOX6 in patients with diabetic kidney disease and their correlation with renal function

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Abstract: Objective To investigate the serum levels of EZH2 (enhancer of zeste homolog 2) and SOX6 (sex - determining region Y-box protein 6) in diabetic kidney disease (DKD) patients and their correlation with disease severity and renal function. **Methods** A retrospective study was conducted on 120 patients with DKD admitted to Zigong First People's Hospital from December 2021 to December 2023 (DKD group), and 120 patients with simple diabetes were included as the diabetic group. Clinical data were collected, and enzyme-linked immunosorbent assay (ELISA) was used to measure the serum levels of EZH2 and SOX6. A fully automated biochemical analyzer was used to determine the 24 - hour urine protein quantity (24 h Upro), serum creatinine (Scr), cystatin - C (Cys - C), and blood urea nitrogen (BUN), urine albumin-to-creatinine ratio (UACR) levels. According to the estimated glomerular filtration rate (eGFR) , patients in the DKD group were divided into mild group [60-89 mL/(min·1.73m^2), n=47] , moderate group [30 - < 60 mL/(min·1.73 m^2), n=40], and severe group[< 30 mL/(min·1.73m^2), n=33]. Multivariate logistic regression analysis was performed to identify the influencing factors of disease severity in DKD patients. Spearman and Pearson correlation analyses were used to evaluate the correlation of serum EZH2, SOX6 expression levels with disease severity and renal function indicators. **Results** Compared with the diabetic group, the DKD group had significantly higher serum levels of EZH2[(26.52±5.25) pg/mL *vs* (4.13±0.62) pg/mL, t=46.396, P<0.01] and SOX6[(16.44 ± 3.18) pg/mL *vs* (7.19 ± 1.24) pg/mL, t=29.687, P<0.01]. As the severity of DKD increased (mild group→ moderate group→ severe group), levels of BUN, Cys-C, Scr, 24 h Upro, EZH2, SOX6, and UACR increased (P<0.05). Multivariate logistic regression analysis showed that high levels of BUN, Cys-C, Scr, 24 h Upro, EZH2, SOX6, and UACR were risk factors for the severity of DKD (P<0.05). In patients with DKD serum EZH2 and SOX6 levels were positively correlated with disease severity and renal function indicators (BUN, Cys-C, Scr, 24 h Upro), respectively (P<0.05). **Conclusion** The serum levels of EZH2 and SOX6 are elevated in DKD patients, and both are respectively associated with the progression of DKD and renal dysfunction.

Keywords: Enhancer of zeste homolog 2; Sex-determining region Y box protein 6; Diabetic kidney disease; Renal function; Glomerular filtration rate

The incidence of diabetes mellitus has been increasing annually over the past few decades. Diabetic nephropathy (DN) is a microvascular complication of diabetes mellitus, characterized primarily by glomerulosclerosis. With the progression of inflammation, renal cell fibrosis, and renal cell dysfunction, the mortality rate of patients with DN is significantly increased [1]. In-depth study of the pathogenesis of DN and identification of effective early diagnostic markers and therapeutic targets are of great clinical significance [2]. Enhancer of zeste homolog 2 (EZH2) is mainly involved in DNA methylation. Studies have shown that EZH2 accumulates in high glucose-induced mouse glomerular mesangial cell line SV40-MES-13, accompanied by increased cell proliferation, inflammatory factor release, and fibrosis, which can promote the progression of DN [3]. Sex-determining region Y box protein 6 (SOX6) is an important member of the SOX gene family. Its expression is upregulated in high glucose-induced mesangial cells, and inhibition of SOX6 expression can alleviate cell proliferation, fibrosis, and inflammation [4]. However, few studies have investigated the expression levels and effects of EZH2 and SOX6 in patients with DN. Therefore, this study detected the serum levels of EZH2 and SOX6 in patients with DN and analyzed their correlation with renal function. The results are reported as follows.

1 Materials and Methods

1.1 General Information

A total of 120 patients with DN admitted to the Department of Endocrinology, The First People's Hospital of Zigong City from December 2021 to December 2023 were selected as the observation objects (DN group), including 63 males and 57 females, with an age of (61.94±8.06) years. Inclusion criteria: (1) Type 2 diabetes mellitus, conforming to the diagnostic criteria of DN [5]; (2) Estimated glomerular filtration rate (eGFR) ≤ 90 mL/(min • 1.73 m^2); (3) Age ≥18 years; (4) Complete clinical data. Exclusion criteria: (1) Type 1 diabetes mellitus or special types of diabetes mellitus; (2) Complicated with autoimmune diseases, infections, malignant tumors, or hyperthyroidism; (3) A history of renal surgery or dialysis, or complicated with renal trauma, acute/chronic nephritis, or

other renal diseases; (4) Severe psychotropic drug dependence; (5) Sensory or motor nerve dysfunction not caused by diabetes mellitus.

A total of 120 patients with simple diabetes mellitus who met the *Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition)* [6] in the same hospital during the same period were enrolled as the diabetes mellitus group, including 66 males and 54 females, with an age of (61.68±7.95) years. Inclusion criteria: Confirmed type 2 diabetes mellitus. Exclusion criteria: Same as those for the DN group. There was no statistically significant difference in gender or age between the two groups (P>0.05). This study was reviewed and approved by the Ethics Committee of The First People's Hospital of Zigong City [Ethics Approval No. (Research) 108, 2021].

1.2 Methods

1.2.1 Detection of Serum EZH2 and SOX6 Levels

Fasting peripheral venous blood was collected from the subjects on the next morning after admission (before treatment). The blood samples were centrifuged at 3000 r/min (centrifugal radius: 8 cm) for 30 min to separate serum. Serum samples were diluted 1:1 with normal saline. An appropriate amount of serum was added to enzyme-linked immunosorbent assay (ELISA) kits (KeAiBo Biotechnology, catalog numbers: CB20927-Hu, CB20831-Hu). After sequential incubation with enzyme-labeled antibody, substrate chromogenic solution, and stop solution, the absorbance was measured at 450 nm using a microplate reader (Qingdao Juchuang Jiaheng Analytical Instrument Co., Ltd., catalog number: HBS-1096C). A standard concentration-absorbance curve was plotted to calculate the levels of EZH2 and SOX6 in the samples.

1.2.2 Determination of Renal Function Indicators

Fasting peripheral venous blood and 24-hour urine samples were collected from patients in the DN group on the next morning after admission. An automatic biochemical analyzer (Beideng Medical, catalog number: BS-280) was used to determine the levels of 24-hour urine protein (24 h Upro), serum creatinine (Scr), cystatin-C (Cys-C), blood urea nitrogen (BUN), and urinary albumin-to-creatinine ratio (UACR) by turbidimetry, picric acid rate method, immunoturbidimetry, enzyme-coupled rate method, and enzyme method, respectively.

1.2.3 Collection of Clinical Data

Clinical data of the enrolled subjects were collected through the medical record system of The First People's Hospital of Zigong City, including body mass index (BMI), age, duration of diabetes mellitus, smoking history, gender, and drinking history.

1.2.4 Assessment of Disease Severity in Patients with DN

The disease severity of patients with DN was assessed according to eGFR levels and divided into three groups: mild group [60-89 mL/(min·1.73 m²), n=47], moderate group [30-<60 mL/(min·1.73 m²), n=40], and severe group [<30 mL/(min·1.73 m²), n=33] [7].

1.3 Statistical Methods

SPSS 25.0 software was used for data analysis. Measurement data conforming to normal distribution were expressed as $\bar{x}\pm s$. Independent samples t-test was used for comparison between two groups, one-way analysis of variance (ANOVA) was used for comparison among three groups, and LSD-t test was used for pairwise comparison. Count data were expressed as cases (%), and χ^2 test was used for comparison. Multivariate logistic regression analysis was used to identify the influencing factors of disease severity in patients with DN. Spearman and Pearson correlation analyses were used to evaluate the correlation between serum EZH2/SOX6 levels and disease severity/renal function indicators in the DN group. A P-value <0.05 was considered statistically significant.

2 Results

2.1 Comparison of Serum EZH2 and SOX6 Levels Between the Diabetes Mellitus Group and DN Group

Compared with the diabetes mellitus group, the DN group had significantly higher serum levels of EZH2 [(26.52 ± 5.25) pg/mL *vs* (4.13 ± 0.62) pg/mL, t=46.396, P<0.01] and SOX6 [(16.44 ± 3.18) pg/mL *vs* (7.19±1.24) pg/mL, t=29.687, P<0.01].

2.2 Comparison of Clinical Data and Serum EZH2/SOX6 Levels Among DN Patients with Different Disease Severities

There were no statistically significant differences in drinking history, age, smoking history, BMI, gender, or duration of diabetes mellitus among DN patients with different disease severities (P>0.05). Compared with the mild group, the moderate and severe groups had significantly higher levels of BUN, Cys-C, Scr, 24 h Upro, EZH2, SOX6, and UACR (P<0.05). Compared with the moderate group, the severe group had significantly higher levels of BUN, Cys-C, Scr, 24 h Upro, EZH2, SOX6, and UACR (P<0.05). See **Table 1.**

2.3 Multivariate Logistic Regression Analysis of Influencing Factors for Disease Severity

Taking the disease severity of DN patients (severe=1; mild/moderate=0) as the dependent variable, and BUN (measured value), Cys-C (measured value), Scr (measured value), 24 h Upro (measured value), EZH2 (measured value), SOX6 (measured value), and UACR (measured value) as independent variables, multivariate logistic regression analysis was performed. The results showed that increased levels of BUN, Cys-C, Scr, 24 h Upro, EZH2, SOX6, and UACR were risk factors for increased disease severity (P<0.05). See **Table 2.**

Tab.1 Comparison of clinical data，serum EZH2 and SOX6 of diabetic kidney disease patients with different disease severity （$\bar{x}\pm s$）

Item	Mild group (n=47)	Moderate group (n=40)	Severe group (n=33)	F/χ^2 value	P value
Age (years)	61.13±7.95	61.60±8.01	63.51±8.19	0.904	0.408
Gender [case(%)]				0.165	0.921
Male	25 (53.19)	20 (50.00)	18 (54.55)		
Female	22 (46.81)	20 (50.00)	15 (45.45)		
BMI (kg/m²)	24.25±3.01	24.31±3.14	24.66±3.57	0.173	0.841
Duration of diabetes (years)	6.68±1.02	6.75±1.34	6.98±1.10	0.681	0.508
Smoking history [case(%)]	14 (29.79)	13 (32.50)	9 (27.27)	0.237	0.888
Drinking history [case(%)]	15 (31.91)	13 (32.50)	12 (36.36)	0.191	0.909
BUN (mmol/L)	347.21±44.20	429.20±58.11[a]	491.25±63.01[ab]	69.78	<0.001
Cys-C (mg/L)	1.27±0.20	1.56±0.27[a]	1.87±0.25[ab]	71.778	<0.001
Scr (μmol/L)	109.31±16.88	191.23±22.90[a]	224.17±36.56[ab]	95.09	<0.001
24 h Upro (g)	0.66±0.12	0.90±0.14[a]	1.35±0.22[ab]	182.513	<0.001
EZH2 (pg/mL)	21.58±3.20	26.60±3.29[a]	33.46±4.64[ab]	101.188	<0.001
SOX6 (pg/mL)	13.69±1.51	16.28±2.16[a]	20.55±2.82[ab]	98.765	<0.001
UACR (mg/g)	39.16±5.51	67.39±12.45[a]	92.19±13.60[ab]	247.145	<0.001

2.4 Correlation Between Serum EZH2/SOX6 Levels and Disease Severity/Renal Function Indicators in DN Patients

Serum EZH2 and SOX6 levels were positively correlated with disease severity and renal function indicators (BUN, Cys-C, Scr, 24 h Upro) in DN patients (P<0.05). See **Table 3.**

Tab.2 Multivariate logistic regression analysis of the disease severity of diabetic kidney disease patients

Factor	*B*	*SE*	*Wald* χ^2	*OR*	*95%CI*	*P* value
BUN	0.790	0.336	5.532	2.204	1.141-4.258	0.019
Cys-C	0.710	0.198	12.841	2.033	1.379-2.997	＜0.001
Scr	0.768	0.185	17.245	2.156	1.500-3.098	＜0.001
24 h Upro	0.975	0.263	13.752	2.652	1.584-4.441	＜0.001
EZH2	1.135	0.394	8.293	3.110	1.437-6.732	0.004
SOX6	0.880	0.242	13.212	2.410	1.500-3.873	＜0.001
UACR	0.773	0.271	8.134	2.166	1.273-3.684	0.004

Tab.3 Correlation between serum EZH2，SOX6 levels and disease severity and renal function in patients with diabetic kidney disease

Indicator	EZH2		SOX6	
	r value	*P* value	*r* value	*P* value
Disease severity	0.628	＜0.001	0.515	＜0.001
BUN	0.469	＜0.001	0.469	＜0.001
Cys-C	0.415	＜0.001	0.415	＜0.001
Scr	0.387	＜0.001	0.387	＜0.001
24 h Upro	0.562	＜0.001	0.562	＜0.001

3 Discussion

Chronic complications of diabetes mellitus are a global health problem. DN is a common cause of chronic kidney disease worldwide, but the molecular mechanism of DN remains poorly understood, which hinders the implementation of effective therapeutic strategies [8]. Early assessment of disease status through effective biomarkers can prevent/delay the occurrence of DN and reduce the renal burden of diabetic patients [9].

The *EZH2* gene is located on chromosome 7q35 and can encode multiple amino acids. The EZH2 subunit alone lacks histone methyltransferase activity and requires binding to the *EED* interaction domain (EID) or cysteine-rich domain to exert its function. Its main function is to catalyze the methylation of histone H3 and inhibit the transcription of target genes [10]. β-cells are endocrine cells responsible for insulin storage, synthesis, and secretion. In diabetic patients, β-cell function is selectively impaired, leading to dependence on exogenous insulin. Studies have found that EZH2 inhibitors such as GSK126 and tazemetostat can induce the transformation of cell phenotype to β-like cell characteristics. Targeted inhibition of EZH2 is key to realizing the regenerative potential of β-cells, thereby restoring the insulin-producing capacity of β-like cells [11]. EZH2 expression is increased in animal models of renal injury. It participates in inhibiting mesangial cell fibrosis by catalyzing H3K27me3, maintains low and stable levels of inflammatory genes, and thus protects renal function. Activation of EZH2 may cause focal segmental glomerulosclerosis, inhibition of epidermal growth factor and platelet-derived growth factor receptor expression, inactivation of multiple signaling pathways, and renal fibrosis [12-13]. In this study, by analyzing serum EZH2 levels in diabetic patients and DN patients, we found that EZH2 levels were higher in DN patients. BUN, Cys-C, Scr, 24 h Upro, EZH2, and UACR were risk factors for disease severity in DN patients, and serum EZH2 levels in DN patients were positively correlated with disease severity and renal function indicators.

The SOX family includes transcription factors SOX5, SOX6, SOX13, and SOX23. SOX6 contains a DNA-binding domain and exerts gene regulatory effects by binding to the minor groove of DNA or interacting with cofactors. SOX6 can regulate adipogenesis in vertebrates by inducing adiporegulators (peroxisome proliferator-activated receptors), CCAAT enhancer-binding protein alpha (C/EBPα), and mesoderm specific transcript (MEST). SOX6 also has insulin-regulating function: the insulin promoter contains binding sites for pancreatic and duodenal homebox factor-1 (PDX1) and SOX6, and SOX6 binding reduces insulin secretion [14-15]. Shu et al. [16] used high glucose to culture human mesangial cells (HMCs) to establish a cellular model of DN. Overexpression of SOX6 was directly associated with increased oxidative stress, extracellular matrix deposition, and inflammatory response in HMCs, and also caused extracellular matrix deposition and apoptosis in proximal tubular epithelial cells of the renal cortex [17]. In addition, fibrosis occurs in renal tissues of DN mice and high glucose-induced mouse mesangial cells, which predicts

subsequent renal sclerosis and renal dysfunction. Inhibition of SOX6 expression improves high glucose-induced renal interstitial fibrosis by targeting microRNA (miR)-342-3p and miR-223-3p, suggesting that targeting SOX6 may be a new therapeutic target for DN [18-19]. In this study, serum SOX6 levels in DN patients were significantly higher than those in patients with simple diabetes mellitus. SOX6 was an effective factor affecting the disease severity of DN patients, and serum SOX6 levels increased with the aggravation of disease severity and the increase of renal function indicators.

In conclusion, serum EZH2 and SOX6 levels are increased in DN patients, and both are correlated with DN progression and renal function decline. Clinically, detecting serum EZH2 and SOX6 levels in DN patients may be helpful for disease assessment and selection of subsequent therapeutic measures. This study has limitations: it did not evaluate the intervention effect by targeting EZH2 and SOX6 expression, which needs to be supplemented in future studies.

Conflict of interest None

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·论　著·

EZH2 和 SOX6 在糖尿病肾病患者中的表达及与肾功能的相关性研究

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摘要：目的　探讨Zeste同源蛋白增强子2（EZH2）和性别决定区域Y盒蛋白6（SOX6）在糖尿病肾病患者血清中的水平及与病情严重程度和肾功能的相关性。**方法**　选择2021年12月至2023年12月自贡市第一人民医院收治的120例糖尿病肾病患者作为回顾性研究的观察对象（糖尿病肾病组），纳入同期同院收治的120例单纯糖尿病患者作为糖尿病组。收集患者的临床资料，采用酶联免疫吸附试验检测血清EZH2和SOX6水平，全自动生化分析仪测定患者24 h尿蛋白定量（24 h Upro）、血清肌酐（Scr）、胱抑素-C（Cys-C）、血尿素氮（BUN）、尿白蛋白/尿肌酐比值（UACR）水平。根据估算肾小球滤过率（eGFR）将糖尿病肾病患者分为轻度组［60~ < 90 mL/（min·1.73 m^2），n=47］、中度组［30~ < 60 mL/（min·1.73 m^2），n=40］、重度组［ < 30 mL/（min·1.73 m^2），n=33］。采用多因素logistic回归分析糖尿病肾病患者病情严重程度的影响因素，采用Spearman与Pearson相关性分析血清EZH2、SOX6水平与糖尿病肾病患者病情严重程度、肾功能指标的相关性。**结果**　与糖尿病组比较，糖尿病肾病组患者血清EZH2［（26.52±5.25）pg/mL *vs*（4.13±0.62）pg/mL，t=46.396，P < 0.01］、SOX6［（16.44±3.18）pg/mL *vs*（7.19±1.24）pg/mL，t=29.687，P < 0.01］水平均较高。随着糖尿病肾病患者疾病严重程度的提高（轻度组→中度组→重度组），BUN、Cys-C、Scr、24 h Upro、EZH2、SOX6、UACR水平升高（P < 0.05）。多因素logistic回归分析显示高水平的BUN、Cys-C、Scr、24 h Upro、EZH2、SOX6、UACR是糖尿病肾病患者病情严重程度的危险因素（P < 0.05）。糖尿病肾病患者血清EZH2、SOX6水平分别与病情严重程度以及肾功能指标（BUN、Cys-C、Scr、24 h Upro）水平呈正相关（P < 0.05）。**结论**　糖尿病肾病患者血清EZH2、SOX6水平均升高，二者均与糖尿病肾病进展及肾功能减退相关。

关键词：Zeste同源蛋白增强子2；性别决定区域Y盒蛋白6；糖尿病肾病；肾功能；肾小球滤过率
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Expression of EZH2 and SOX6 in patients with diabetic kidney disease and their correlation with renal function

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Abstract: Objective　To investigate the serum levels of enhancer of zeste homolog 2 (EZH2) and sex-determining region Y box protein 6 (SOX6) in diabetic kidney disease (DKD) patients and their correlation with disease severity and renal function. **Methods**　A retrospective study was conducted on 120 patients with DKD admitted to Zigong First People's Hospital from December 2021 to December 2023 (DKD group), and 120 patients with simple diabetes were included as the diabetic group. Clinical data were collected, and enzyme-linked immunosorbent assay (ELISA) was used to measure the serum levels of EZH2 and SOX6. A fully automated biochemical analyzer was used to determine the 24-hour urine protein quantity (24 h Upro), serum creatinine (Scr), cystatin-C (Cys-C), and blood urea nitrogen (BUN), urine albumin-to-creatinine ratio (UACR) levels. According to the estimated glomerular filtration rate (eGFR), patients in the DKD group were divided into mild group [60- < 90 mL/(min·1.73 m^2), n=47], moderate group [30- < 60 mL/(min·1.73 m^2), n=40], and severe group [< 30 mL/(min·1.73 m^2), n=33]. Multivariate logistic

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regression analysis was performed to identify the influencing factors of disease severity in DKD patients. Spearman and Pearson correlation analyses were used to evaluate the correlation of serum EZH2, SOX6 levels with disease severity and renal function indicators. **Results** Compared with the diabetic group, the DKD group had significantly higher serum levels of EZH2 [(26.52±5.25) pg/mL *vs* (4.13±0.62) pg/mL, t=46.396, P<0.01] and SOX6[(16.44±3.18) pg/mL *vs* (7.19±1.24) pg/mL, t=29.687, P<0.01]. As the severity of DKD increased (mild group→ moderate group→ severe group), levels of BUN, Cys-C, Scr, 24 h Upro, EZH2, SOX6, and UACR increased (P<0.05). Multivariate logistic regression analysis showed that high levels of BUN, Cys-C, Scr, 24 h Upro, EZH2, SOX6, and UACR were risk factors for the severity of DKD (P<0.05). In patients with DKD, serum EZH2 and SOX6 levels were positively correlated with disease severity and renal function indicators (BUN, Cys-C, Scr, 24 h Upro), respectively (P<0.05). **Conclusion** The serum levels of EZH2 and SOX6 are elevated in DKD patients, and both are respectively associated with the progression of DKD and renal dysfunction.

Keywords: Enhancer of zeste homolog 2; Sex-determining region Y box protein 6; Diabetic kidney disease; Renal function; Glomerular filtration rate

过去几十年,糖尿病的发病率逐年增加。糖尿病肾病是糖尿病的微血管并发症,最主要特征是肾小球硬化,随着炎症、肾脏细胞纤维化、肾脏细胞功能障碍的进展,大大增加了糖尿病肾病患者的死亡率[1]。深入研究糖尿病肾病的发病机制,寻找有效的早期诊断标志物和治疗靶点具有重要的临床意义[2]。Zeste同源蛋白增强子2(enhancer of zeste homolog 2, EZH2)主要参与DNA甲基化,有研究指出,高糖诱导的小鼠肾小球系膜细胞SV40-MES-13中EZH2聚集,细胞增殖、炎症因子释放和纤维化程度增加,可促进糖尿病肾病进展[3]。性别决定区域Y盒蛋白6(sex-determining region Y box protein 6,SOX6)是SOX基因家族的重要成员,在高糖诱导的系膜细胞中表达升高,抑制SOX6的表达可以缓解细胞的增殖、纤维化和炎症[4]。糖尿病肾病患者中EZH2和SOX6的表达水平及影响少有研究,因此,本研究将检测糖尿病肾病患者血清中EZH2和SOX6的表达水平,分析二者与患者肾功能的关系,报道如下。

1 资料与方法

1.1 一般资料 选择2021年12月至2023年12月自贡市第一人民医院收治的120例糖尿病肾病患者作为观察对象(糖尿病肾病组),男63例,女57例,年龄(61.94±8.06)岁。纳入标准:(1)2型糖尿病,符合糖尿病肾病诊断标准[5];(2)估算肾小球滤过率(estimated glomerular filtration rate,eGFR)≤90 mL/(min·1.73 m^2);(3)年龄≥18周岁;(4)资料齐全,完整。排除标准:(1)1型糖尿病或及特殊类型糖尿病;(2)合并自身免疫性疾病、感染、恶性肿瘤、甲状腺功能亢进;(3)既往有肾脏手术、透析史,合并肾脏外伤、急/慢性肾炎等肾脏疾病;(4)存在严重精神药物依赖;(5)非糖尿病引起的感觉、运动神经功能障碍。纳入同期同院120例符合《中国2型糖尿病防治指南(2020年版)》[6]的单纯糖尿病患者作为糖尿病组,男66例,女54例,年龄(61.68±7.95)岁。纳入标准:确诊均为2型糖尿病。排除标准同糖尿病肾病组。两组受试者性别、年龄的比较,差异无统计学意义(P>0.05)。本研究经自贡市第一人民医院伦理委员会审核批准[伦审(研)2021年第108号]。

1.2 *方法*

1.2.1 血清EZH2、SOX6水平检测 采集受试者入院次日(治疗前)晨起空腹外周静脉血,以转速3 000 r/min(离心半径8 cm)离心30 min,分离血清,使用生理盐水1∶1稀释血清样本,取适量血清加入酶联免疫吸附法(enzyme-linked immunosorbent assay,ELISA)试剂盒(科艾博生物,货号:CB20927-Hu、CB20831-Hu),依次经过酶标抗体、底物显色液、终止反应液孵育,在酶标仪(青岛聚创嘉恒分析仪器有限公司,货号:HBS-1096C)450 nm波长处测定吸光度,绘制标准品浓度-吸光度曲线,计算样本中EZH2、SOX6的水平。

1.2.2 肾功能指标测定 采集糖尿病肾病患者入院次日空腹外周静脉血和24 h尿液,使用全自动生化分析仪(贝登医疗,货号:BS-280)分别以比浊法、苦味酸速率法、免疫透射比浊法、酶偶联速率法、酶法测定24 h尿蛋白定量(24-hour urine protein,24 h Upro)、血清肌酐(serum creatinine,Scr)、胱抑素-C(cystatin-C,Cys-C)、血尿素氮(blood urea nitrogen,BUN)、尿白蛋白/尿肌酐比值(urinary albumin-to-creatinine ratio,UACR)水平。

1.2.3 收集临床资料 通过自贡市第一人民医院病历系统收集入组受试者的临床资料,包括身体质量指数(body mass index,BMI)、年龄、性别、糖尿病病程、吸烟史、饮酒史。

1.2.4　糖尿病肾病患者病情严重程度评估　根据糖尿病肾病患者 eGFR 水平评估病情严重程度，分为 3 组：轻度组[60～<90 mL/(min·1.73 m^2)，n=47]、中度组[30～<60 mL/(min·1.73 m^2)，n=40]、重度组[<30 mL/(min·1.73 m^2)，n=33][7]。

1.3　统计学方法　采用 SPSS 25.0 软件分析数据，计量资料符合正态分布以 $\bar{x}\pm s$ 表示，两组间比较使用独立样本 t 检验，三组间比较使用单因素方差分析，两两比较采用 LSD-t 检验；计数资料以例(%)表示，采用 χ^2 检验；采用 logistic 多因素回归分析糖尿病肾病患者病情严重程度的影响因素，糖尿病肾病组血清 EZH2、SOX6 表达水平与患者病情严重程度、肾功能指标的相关性采用 Spearman 及 Pearson 相关性分析；P<0.05 表示差异有统计学意义。

2　结　果

2.1　糖尿病组和糖尿病肾病组血清 EZH2、SOX6 水平比较　与糖尿病组比较，糖尿病肾病组患者血清 EZH2[(26.52±5.25) pg/mL *vs* (4.13±0.62) pg/mL，t=46.396，P<0.01]、SOX6[(16.44±3.18) pg/mL *vs* (7.19±1.24) pg/mL，t=29.687，P<0.01]水平均较高。

2.2　不同病情严重程度糖尿病肾病患者临床资料及血清 EZH2、SOX6 比较　不同病情严重程度糖尿病肾病患者饮酒史、年龄、吸烟史、BMI、性别、糖尿病病程比较，差异无统计学意义(P>0.05)。与轻度组比较，中度、重度组 BUN、Cys-C、Scr、24 h Upro、EZH2、SOX6、UACR 均更高(P<0.05)；与中度组比较，重度组 BUN、Cys-C、Scr、24 h Upro、EZH2、SOX6、UACR 均更高(P<0.05)。见表 1。

2.3　影响糖尿病肾病患者病情严重程度的多因素 logistic 回归分析　以糖尿病肾病患者病情严重程度(重度=1；轻度、中度=0)为因变量，以 BUN(实测值)、Cys-C(实测值)、Scr(实测值)、24 h Upro(实测值)、EZH2(实测值)、SOX6(实测值)、UACR(实测值)为自变量行多因素 logistic 回归分析，结果显示，BUN、Cys-C、Scr、24 h Upro、EZH2、SOX6、UACR 水平升高是病情严重程度加重的危险因素(P<0.05)。见表 2。

2.4　血清 EZH2、SOX6 水平与糖尿病肾病患者病情严重程度和肾功能指标水平的相关性　血清 EZH2、SOX6 水平分别与糖尿病肾病患者病情严重程度和肾功能指标(BUN、Cys-C、Scr、24 h Upro)水平呈正相关(P<0.05)。见表 3。

表 1　不同病情严重程度糖尿病肾病患者临床资料及血清 EZH2、SOX6 比较　($\bar{x}\pm s$)

Tab.1　Comparison of clinical data, serum EZH2 and SOX6 of diabetic kidney disease patients with different disease severity　($\bar{x}\pm s$)

项目	轻度组(n=47)	中度组(n=40)	重度组(n=33)	F/χ^2 值	P 值
年龄(岁)	61.13±7.95	61.60±8.01	63.51±8.19	0.904	0.408
性别[例(%)]					
男	25(53.19)	20(50.00)	18(54.55)	0.165	0.921
女	22(46.81)	20(50.00)	15(45.45)		
BMI(kg/m^2)	24.25±3.01	24.31±3.14	24.66±3.57	0.173	0.841
糖尿病病程(年)	6.68±1.02	6.75±1.34	6.98±1.10	0.681	0.508
吸烟史[例(%)]	14(29.79)	13(32.50)	9(27.27)	0.237	0.888
饮酒史[例(%)]	15(31.91)	13(32.50)	12(36.36)	0.191	0.909
BUN(mmol/L)	347.21±44.20	429.20±58.11[a]	491.25±63.01[ab]	69.780	<0.001
Cys-C(mg/L)	1.27±0.20	1.56±0.22[a]	1.87±0.25[ab]	71.778	<0.001
Scr(μmol/L)	109.31±16.88	191.23±27.90[a]	224.17±36.56[ab]	195.090	<0.001
24 h Upro(g)	0.66±0.12	0.90±0.14[a]	1.35±0.22[ab]	182.513	<0.001
EZH2(pg/mL)	21.58±3.20	26.60±3.29[a]	33.46±4.64[ab]	101.188	<0.001
SOX6(pg/mL)	13.69±1.51	16.28±2.16[a]	20.55±2.82[ab]	98.765	<0.001
UACR(mg/g)	39.16±5.10	67.39±12.45[a]	92.19±13.60[ab]	247.145	<0.001

注：与轻度组比较，[a]P<0.05；与中度组比较，[b]P<0.05。

表 2　影响糖尿病肾病患者病情严重程度的多因素 logistic 回归分析

Tab.2　Multivariate logistic regression analysis of the disease severity of diabetic kidney disease patients

影响因素	β	SE	Wald χ^2	OR 值	95%CI	P 值
BUN	0.790	0.336	5.532	2.204	1.141~4.258	0.019
Cys-C	0.710	0.198	12.841	2.033	1.379~2.997	<0.001
Scr	0.768	0.185	17.245	2.156	1.500~3.098	<0.001
24 h Upro	0.975	0.263	13.752	2.652	1.584~4.441	<0.001
EZH2	1.135	0.394	8.293	3.110	1.437~6.732	0.004
SOX6	0.880	0.242	13.212	2.410	1.500~3.873	<0.001
UACR	0.773	0.271	8.134	2.166	1.273~3.684	0.004

表 3　血清 EZH2、SOX6 水平与糖尿病肾病病情严重程度和肾功能指标水平的相关性

Tab.3　Correlation of serum EZH2, SOX6 levels with disease severity and renal function in diabetic kidney disease

指标	EZH2		SOX6	
	r 值	P 值	r 值	P 值
病情严重程度	0.628	<0.001	0.515	<0.001
BUN	0.469	<0.001	0.469	<0.001
Cys-C	0.415	<0.001	0.415	<0.001
Scr	0.387	<0.001	0.387	<0.001
24 h Upro	0.562	<0.001	0.562	<0.001

3 讨 论

糖尿病慢性并发症是一个全球性的卫生问题，糖尿病肾病是世界范围内患慢性肾脏疾病的常见原因，但目前对糖尿病肾病发生的分子机制知之甚少，不利于实施有效的治疗策略[8]。通过有效生物标志物评价尽早判断病情，可以预防/延迟糖尿病肾病的发生，降低糖尿病患者的肾脏负担[9]。

*EZH2*基因位于染色体7q35上，可以编码多个氨基酸，单独的EZH2亚基缺乏组蛋白甲基转移酶活性，需要与胚胎外胚层发育蛋白相互作用域(embryonic ectoderm development interaction domain，EID)或富含半胱氨酸的作用域结合才能发挥功能，其主要功能是催化组蛋白H3的甲基化，抑制靶基因的转录[10]。β细胞是负责储存、合成、释放胰岛素的一类内分泌细胞，糖尿病患者β细胞功能被选择性破坏，导致患者需要依赖外源性胰岛素。研究发现，EZH2抑制剂GSK126、他泽司他(tazemetostat)可以促使细胞表型向β样细胞特性转变，靶向抑制EZH2是实现β细胞再生潜能的关键，进而可以恢复β样细胞生产胰岛素的能力[11]。EZH2在肾脏损伤动物模型中表达增加，通过催化H3K27me3参与抑制血管系膜细胞纤维化，维持炎症基因的低水平和稳定状态，以保证肾功能；激活EZH2可能引起局灶节段性肾小球硬化、表皮生长因子及血小板源性生长因子受体表达抑制、多种信号途径失活以及肾纤维化[12-13]。本研究通过分析糖尿病患者和糖尿病肾病患者血清EZH2的水平发现，EZH2在糖尿病肾病患者中水平更高，BUN、Cys-C、Scr、24 h Upro、EZH2、UACR是影响糖尿病肾病患者病情严重程度的危险因素，且糖尿病肾病患者血清EZH2水平与患者病情严重程度和肾功能指标呈正相关。

SOX家族包括转录因子SOX5、SOX6、SOX13和SOX23，SOX6含有DNA结合域，通过与DNA小沟槽结合或与辅助因子相互作用发挥基因调控作用。SOX6可以诱导脂肪调节剂(过氧化物酶体增殖物激活受体)、CCAAT-增强子结合蛋白(CCAAT enhancer-binding protein alpha，C/EBPα)及中胚层特异性转录酶(mesoderm specific transcrip，MEST)来调节脊椎动物的脂肪生成。SOX6还具有调节胰岛素的功能，胰岛素启动子含有抑制胰腺十二指肠同源盒因子-1(pancreatic and duodenal homebox faetor-1，PDX1)和SOX6的结合部位进而减少胰岛素的分泌[14-15]。Shu等[16]采用高糖培养人肾小球系膜细胞(human mesangial cells，HMCs)模拟糖尿病肾病细胞模型，SOX6过表达直接与HMCs细胞氧化应激、细胞外基质沉积和炎症反应加剧有关，还会造成肾皮质近曲小管上皮细胞外基质沉积和细胞凋亡[17]。此外，糖尿病肾病小鼠肾组织和高糖诱导的小鼠肾系膜细胞中均出现纤维化现象，这预示着接下来的肾脏硬化和肾功能障碍，抑制SOX6的表达通过靶向微小RNA(micro RNA，miR)-342-3p、miR-223-3p改善了高糖诱导的肾间质纤维化，靶向SOX6可能作为治疗糖尿病肾病的新靶点[18-19]。本研究中，糖尿病肾病患者血清中SOX6的水平显著高于单纯糖尿病患者，SOX6是影响糖尿病肾病患者病情严重程度有效因素，随着糖尿病肾病患者病情严重程度和肾功能指标的增加，血清SOX6的水平升高。

综上所述，糖尿病肾病患者血清EZH2、SOX6水平均升高，二者均与糖尿病肾病进展及肾功能减退相关，临床上通过检测糖尿病肾病患者血清EZH2、SOX6水平可能对疾病的评估和后续治疗措施的选择有所帮助。本研究还存在不足之处，未靶向EZH2、SOX6的表达评价对患者的干预疗效，后续研究需要补充。

利益冲突 无

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[14]研究结果表明，接种训练加弹力带抗阻运动显著改善患者血糖水平。本研究结论与其存在相似之处。这是由于通过控制总能量摄入、减少膳食脂肪比例、增加全谷物和杂豆类食物比例，以及个性化血糖管理方案，有助于改善血糖和血脂水平。中低强度有氧运动如快走、慢跑等，以及适量的抗阻运动如哑铃操，能增加能量消耗，促进脂肪分解，提高心肺耐力和胰岛β细胞功能，从而降低血糖。柔韧性训练如瑜伽、拉伸操等，则能增加关节活动度，减少运动损伤风险。

运动是健康体适能管理的核心，适度锻炼能提高胰岛素敏感性，促进糖分吸收利用，有效控制血糖。运动加速糖分代谢，减少血糖滞留，降低浓度，同时促进胰岛β细胞修复与再生，改善胰岛素抵抗。抗阻运动增加肌肉含量，改善糖脂代谢[15]。健康体适能管理结合饮食控制和运动训练，制定个性化运动处方和饮食计划，确保运动安全有效，控制体重，减少肥胖对血脂的不良影响[16]。相比之下，常规干预中的运动计划可能缺乏科学依据和合理安排。

综上所述，健康体适能管理应用于糖尿病前期患者，可降低血糖，改善血脂和胰岛β功能，减少脂肪沉积，提高肌肉含量。

利益冲突　无

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(上接第1363页)

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