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Relationship of serum miR-93-5p and miR-124-3p levels with short-term progression of albuminuria and prognosis in patients with diabetic nephropathy

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Abstract: **Objective** To measure the expression levels of serum micro RNA (miR)-93-5p and miR-124-3p in patients with diabetic nephropathy (DN), and to explore the relationship of their changes with the short-term progression and prognosis of albuminuria. **Methods** A total of 116 DN patients admitted to Harbin First Hospital between January 2021 and August 2023 were retrospectively selected as DN group, and 120 healthy individuals in the same period were selected as control group. Patients with DN were categorized into a progressive group (32 cases) and a non-progressive group (84 cases) based on the short-term progression of albuminuria. And patients with DN were divided into poor prognosis group (41 cases) and good prognosis group (75 cases) according to whether patients developed end-stage renal disease, renal failure and uremia after one-year follow-up. Fluorescence quantitative polymerase chain reaction was used to detect the levels of serum miR-93-5p and miR-124-3p in the subjects. Multivariate logistic regression analysis was conducted to identify the factors influencing short-term progression of albuminuria and poor prognosis in DN patients. The predictive value of serum miR-93-5p and miR-124-3p levels, individually and combined, for poor prognosis in DN patients was analyzed using receiver operating characteristic (ROC) curve. **Results** The serum levels of miR-93-5p and miR-124-3p were lower in DN group compared to control group ($P<0.05$), were lower in progression group compared to non-progression group ($P<0.05$), and were lower in poor prognosis group than those in good prognosis group ($P<0.05$). Multivariate logistic regression analysis showed that serum levels of miR-93-5p and miR-124-3p were independent factors affecting the short-term progression of albuminuria and poor prognosis in DN patients ($P<0.05$). The combined prediction of poor prognosis in DN patients by these two miRNAs had a higher area under curve (0.945) than that of miR-93-5p (0.856) or miR-124-3p alone (0.852), with statistically significant differences ($Z=2.504$, $P=0.012$; $Z=2.551$, $P=0.011$). **Conclusion** The serum miR-93-5p and miR-124-3p in DN patients are associated with short-term progression and prognosis of albuminuria. The combined testing has a good predictive value for poor prognosis in DN patients. **Keywords:** Diabetic nephropathy; MicroRNA-93-5p; MicroRNA-124-3p; Albuminuria; Short-term progression

Diabetic nephropathy (DN) is a major microvascular complication of diabetes mellitus, and its pathophysiological process involves abnormal expression of various bioactive substances, including chemokines, pro-inflammatory cytokines, and adhesion molecules [1]. The clinical course of DN includes the normoalbuminuric stage, microalbuminuric stage, and macroalbuminuric stage [2]. Increased urinary albumin is an important marker of glomerular injury [2]. Exploring serum biomarkers associated with short-term progression of albuminuria may help facilitate early clinical intervention. MicroRNA (miR)-93-5p can participate in the pathological process of DN through different signaling pathways [3]. Upregulation of miR-93-5p can ameliorate high-glucose-induced proliferation, fibrosis, and inflammation in glomerular mesangial cells [4]. Studies have shown that, under high-glucose and high-lipid conditions, downregulation of miR-124-3p can induce abnormalities in renal tubular epithelial cells, leading to mitochondrial dysfunction and promoting the development of DN [5]. miR-124-3p is involved in the progression of various kidney diseases, including DN, acute kidney injury, and lupus nephritis, through pathways related to oxidative stress, autophagy, ferroptosis, and

inflammation [6]. At present, the relationship of serum miR-93-5p and miR-124-3p levels with short-term progression of albuminuria and prognosis in patients with DN remains unclear. Therefore, this study was conducted to investigate this issue.

1 Subjects and Methods

1.1 Study Subjects

A total of 116 patients with DN admitted to the Department of Nephrology of Harbin First Hospital from January 2021 to August 2023 were retrospectively selected as the DN group. (1) The inclusion criteria were as follows: ① Diagnosis meeting the criteria for type 2 diabetes mellitus specified in the *Expert Consensus on Hierarchical Diagnosis and Treatment and Quality Management of Type 2 Diabetes* [7]. ② Diagnosis meeting the criteria for DN specified in the *Chinese Clinical Practice Guideline for Diabetic Kidney Disease* [8]. (2) The exclusion criteria were as follows: ① Severe infection, immune system disease, or hematologic disease. ② Concomitant nephritis. Use of drugs affecting renal function within the preceding

3 months. The DN group included 59 women and 57 men, with a mean age of (55.76 ± 5.42) years. During the same period, 120 healthy individuals undergoing physical examination were selected as the control group, including 64 women and 56 men, with a mean age of (56.03 ± 5.47) years. There were no statistically significant differences in sex or age between the two groups ($P > 0.05$). This study was approved by the Medical Ethics Committee of Harbin First Hospital (approval No. 2024-047), and all participants provided informed consent.

1.2 Methods

1.2.1 General Data Collection

After enrollment, clinical data were obtained from the patients' medical records, including age, sex, body mass index (BMI), duration of diabetes, comorbidities [hypertension, hyperlipidemia, and coronary atherosclerotic heart disease (coronary heart disease)], smoking history, drinking history, and family history.

1.2.2 Detection of Serum Indicators

Fasting venous blood samples (4 mL) were collected from patients with DN after admission and before treatment. Blood samples from the control group were collected on the day of physical examination. The samples were allowed to stand at room temperature for 30–60 min and then centrifuged at 2 500 r/min for 10 min with a centrifugation radius of 10 cm. The supernatant was collected and stored at low temperature until use. RNA was extracted from serum and reverse-transcribed into cDNA. Quantitative polymerase chain reaction (qPCR) was used to detect serum miR-93-5p and miR-124-3p levels, with U6 used as the internal reference. The primer sequences [9–10] are shown in **Table 1**, and primer synthesis was completed by Wuhan Jinkairui Bioengineering Co., Ltd. The reaction system consisted of 5 μ L PCR master mix, 3 μ L ddH₂O, 1 μ L primers (0.5 μ L forward primer and 0.5 μ L reverse primer), and 1 μ L cDNA. The amplification protocol was as follows: 95 °C for 52 s, 95 °C for 37 s, 56 °C for 30 s, and 72 °C for 10 s, for a total of 35 cycles.

1.2.3 Assessment of Short-Term Progression of Albuminuria

Patients were dynamically followed and monitored. Data on 24-h urinary albumin and serum creatinine (SCr) were collected at enrollment and again 6 months later. According to the diagnostic criteria for short-term progression of albuminuria [11], patients were divided into a progression group and a non-progression group. Short-term progression of albuminuria was diagnosed if either of the following criteria was met: The first 24-h urinary albumin level was 30–300 mg, and the second 24-h urinary albumin level was >300 mg. The first 24-h urinary albumin level was >300 mg, and the SCr level at the second test was twice that at the first test.

1.2.4 Follow-Up and Prognostic Assessment

Patients were followed for 1 year through outpatient reexamination and telephone follow-up, with follow-up ending in August 2024. According to whether end-stage renal disease, renal failure, or uremia occurred during follow-up, patients were divided into a poor-prognosis group and a good-prognosis group.

1.3 Statistical Analysis

SPSS 24.0 software was used for statistical analysis. Categorical data are expressed as case (%), and comparisons were performed using the χ^2 test. Normally distributed continuous variables are expressed as $\bar{x} \pm s$, and comparisons between two groups were performed using the independent-samples t test. When variances were unequal, the corrected t test was used. Multivariate logistic regression analysis was used to identify factors associated with short-term progression of albuminuria and poor prognosis in patients with DN. ROC curves were plotted to evaluate the predictive value of serum miR-93-5p and miR-124-3p levels, alone and in combination, for poor prognosis in patients with DN. AUCs were compared using the DeLong test. A P value < 0.05 was considered statistically significant.

Table 1. Primer Sequences for Serum miR-93-5p, miR-124-3p, and U6

Primer name	Forward sequence 5'→3'	Reverse sequence 5'→3'
miR-93-5p	ACA CTC CAG CTG GGT CCT GTA CTG ACG TGC CC	CTC AAC TGG TGT CGT GGA
miR-124-3p	TCT TTA AGG CAC GCG GTG	TAT GGT TTT GAC GAC TGT GTG AT
U6	GCT TCG GCA GCA CAT ATA CTA AAA T	CGC TTC ACG AAT TTG CGT GTG TCA T

2 Results

2.1 Comparison of miR-93-5p and miR-124-3p Levels between the DN Group and the Control Group

The serum miR-93-5p level was significantly lower in the DN group than in the control group (0.66 ± 0.11 vs 1.01 ± 0.15 , $P < 0.01$). The serum miR-124-3p level was also significantly lower in the DN group than in the control group (0.80 ± 0.12 vs 1.02 ± 0.13 , $P < 0.01$).

2.2 Comparison of General Data and miR-93-5p and miR-124-3p Levels between the Progression Group and Non-Progression Group

Among the 116 patients with DN, 32 developed short-term progression of albuminuria and were assigned to the progression group, whereas 84 did not develop short-term progression and were assigned to the non-progression group. There was no significant difference in general data between the progression group and the non-progression group ($P > 0.05$). The serum levels of miR-93-5p and miR-124-3p were significantly lower in the progression group than in the non-progression group ($P < 0.05$). See **Table 2**.

2.3 Multivariate Logistic Regression Analysis of Factors Associated with Short-Term Progression of Albuminuria in Patients with DN

Short-term progression of albuminuria in patients with DN was used as the dependent variable (progression=1, non-progression=0), and serum miR-93-5p and miR-124-3p levels were entered as independent variables using their original values. Multivariate logistic regression analysis showed that both serum miR-93-5p and miR-124-3p levels were factors associated with short-term progression of albuminuria in patients with DN ($P<0.05$). See **Table 3**.

2.4 Comparison of General Data and Serum miR-93-5p and miR-124-3p Levels between the Poor-Prognosis and Good-Prognosis Groups

There were no statistically significant differences in general clinical data between the poor-prognosis group and the good-prognosis group ($P>0.05$). The serum levels of miR-93-5p and miR-124-3p were significantly lower in the poor-prognosis group than in the good-prognosis group ($P<0.05$). See **Table 4**.

Table 2. Comparison of General Data and Serum miR-93-5p and miR-124-3p Levels Between the Progression Group and Non-Progression Group [case (%)]

Item	Progression group (n=32)	Non-progression group (n=84)	χ^2/t value	P value
Age			0.639	0.424
≥55 years	12 (37.50)	25 (29.76)		
<55 years	20 (62.50)	59 (70.24)		
Sex			2.395	0.122
Male	12 (37.50)	45 (53.57)		
Female	20 (62.50)	39 (46.43)		
BMI (kg/m ² , $\bar{x}\pm s$)	22.88±2.45	22.35±2.23	1.113	0.268
Duration of diabetes			1.505	0.220
≥10 years	17 (53.13)	34 (40.48)		
<10 years	15 (46.88)	50 (59.52)		
Hypertension	14 (43.75)	30 (35.71)	0.636	0.425
Hyperlipidemia	17 (53.13)	36 (42.86)	0.985	0.321
Coronary heart disease	16 (50.00)	38 (45.24)	0.211	0.646
Smoking history	19 (59.38)	36 (42.86)	2.536	0.111
Drinking history	21 (65.63)	43 (51.19)	1.952	0.162
Family history	17 (53.13)	40 (47.62)	0.281	0.596
miR-93-5p ($\bar{x}\pm s$)	0.52±0.09	0.72±0.12	8.547	<0.001
miR-124-3p ($\bar{x}\pm s$)	0.69±0.10	0.84±0.13	5.891	<0.001

2.5 Multivariate Logistic Regression Analysis of Factors Associated With Poor Prognosis in Patients with DN

Poor prognosis in patients with DN was used as the dependent variable (poor prognosis=1, good prognosis=0), and serum miR-93-5p and miR-124-3p levels, which were statistically significant in univariate analysis, were entered

as independent variables using their original values. Multivariate analysis showed that both serum miR-93-5p and miR-124-3p levels were factors associated with poor prognosis in patients with DN ($P<0.05$). See **Table 5**.

2.6 Predictive Value of miR-93-5p and miR-124-3p Levels for Poor Prognosis in Patients With DN

The AUC of combined serum miR-93-5p and miR-124-3p detection for predicting poor prognosis in patients with DN was higher than that of miR-93-5p alone ($Z=2.504$, $P=0.012$) and higher than that of miR-124-3p alone ($Z=2.551$, $P=0.011$). See **Table 6** and **Figure 1**.

Table 3. Analysis of Factors Associated with Short-Term Progression of Albuminuria in Patients With DN

Variable	β	SE	Wald χ^2	P value	OR	95% CI
miR-93-5p	-1.168	0.237	24.286	<0.001	0.311	0.195–0.495
miR-124-3p	-0.901	0.337	7.154	0.007	0.406	0.210–0.786

Table 4. Comparison of General Data and Serum miR-93-5p and miR-124-3p Levels Between the Poor-Prognosis Group and Good-Prognosis Group [case (%)]

Item	Poor-prognosis group (n=41)	Good-prognosis group (n=75)	χ^2/t value	P value
Age			0.148	0.701
≥55 years	14 (34.15)	23 (30.67)		
<55 years	27 (65.85)	52 (69.33)		
Sex			0.695	0.404
Male	18 (43.90)	39 (52.00)		
Female	23 (56.10)	36 (48.00)		
BMI (kg/m ²)	22.75±2.38	22.36±2.24	0.877	0.382
Duration of diabetes			2.418	0.120
≥10 years	22 (53.66)	29 (38.67)		
<10 years	19 (46.34)	46 (61.33)		
Hypertension	20 (48.78)	24 (32.00)	3.170	0.075
Hyperlipidemia	22 (53.66)	31 (41.33)	1.623	0.203
Coronary heart disease	24 (56.10)	30 (40.00)	2.768	0.096
Smoking history	23 (56.10)	32 (42.67)	1.918	0.166
Drinking history	27 (65.85)	37 (49.33)	2.925	0.087
Family history	21 (51.22)	36 (48.00)	0.110	0.740
miR-93-5p ($\bar{x}\pm s$)	0.57±0.08	0.71±0.12	7.504	<0.001
miR-124-3p ($\bar{x}\pm s$)	0.70±0.11	0.86±0.13	6.678	<0.001

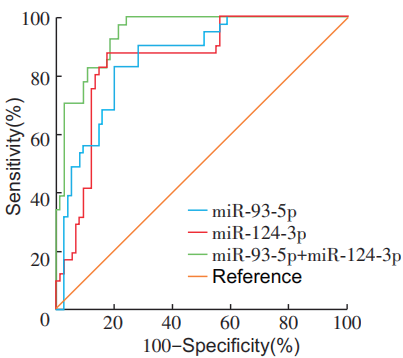


Figure 1 ROC curve of serum miR-93-5p and miR-124-3p levels alone and in combination for predicting poor prognosis in patients with DN

Table 5. Analysis of Factors Associated with Poor Prognosis in Patients With DN

Variable	β	SE	Wald χ^2	P value	OR	95%CI
miR-93-5p	-1.115	0.301	13.716	<0.001	0.328	0.182-0.592
miR-124-3p	-1.149	0.237	23.498	<0.001	0.317	0.199-0.504

Table 6. Predictive Value of Serum miR-93-5p and miR-124-3p Levels for Poor Prognosis in Patients with DN

Indicator	AUC	Cut-off value	Sensitivity (%)	Specificity (%)	95%CI
miR-93-5p	0.856	0.669	82.93	80.00	0.779-0.914
miR-124-3p	0.852	0.795	87.80	82.67	0.774-0.911

3 Discussion

DN, as a complication of diabetes mellitus, poses a major threat to patient survival [1]. At present, the number of patients with diabetes is gradually increasing, and the number of patients with DN is also rising accordingly [12]. The pathological mechanism of DN is complex. Its typical progression is characterized by proteinuria and a decline in glomerular filtration rate [13]. The clinicopathological features of DN include mesangial expansion, tubulointerstitial fibrosis, and thickening of the glomerular basement membrane. Microalbuminuria is the earliest manifestation of DN progression. Microalbuminuria may show intermittent changes. As the disease worsens, hyperglycemia damages the glomerular filtration membrane and increases its pore size. When the filtration rate of plasma albumin exceeds the reabsorptive capacity of the glomerulus, patients enter the stage of overt albuminuria [14]. Albuminuria is one of the best predictors of renal function deterioration. Therefore, it is important to identify serum biomarkers associated with short-term progression of albuminuria [15]. DN progresses rapidly and is often accompanied by other complications. Renal function deteriorates quickly, and patient prognosis is poor. Early prediction of the risk of poor prognosis in patients with DN may help clinicians implement timely interventions and effectively improve prognosis and survival [8]. This study analyzed the relationship of serum miR-93-5p and miR-124-3p levels with short-term progression of albuminuria and prognosis in patients with DN, aiming to assist clinical prognostic evaluation.

miR-93-5p plays a key regulatory role in the occurrence and development of DN. It participates in the pathophysiological process of DN through various mechanisms, including targeted regulation of downstream gene expression [16]. Gu *et al.* [17] showed that miR-93-5p can inhibit high-glucose-induced secretion of inflammatory factors and apoptosis in podocytes, and that this effect is related to miR-93-5p targeting dual-specificity phosphatase 8. In the present study, serum miR-93-5p levels were lower in the DN group than in the control group, consistent with the findings of Wang *et al.* [4], confirming that changes in miR-93-5p levels may be associated with the occurrence of DN. Further analysis according to short-term progression of albuminuria

showed that serum miR-93-5p levels were lower in the progression group than in the non-progression group, suggesting that miR-93-5p may be involved in the short-term progression of albuminuria in patients with DN. Prognostic analysis showed that serum miR-93-5p levels were lower in the poor-prognosis group than in the good-prognosis group, indicating that miR-93-5p levels are associated with prognosis. The mechanism by which miR-93-5p participates in the occurrence and development of DN may be that low miR-93-5p levels weaken the inhibition of inflammatory factor release and oxidative stress, thereby increasing the risk of poor prognosis [18].

miR-124-3p may participate in the occurrence and development of DN by promoting renal fibrosis and chronic inflammatory responses, and its downregulation is associated with chronic inflammation and renal fibrosis in DN [5]. Silencing of the long non-coding RNA KCNQ1OT1 exerts an anti-fibrotic effect by promoting miR-124-3p expression in renal fibrosis, suggesting that it may serve as a potential therapeutic target for renal fibrosis [19]. Lu *et al.* [20] also found that lncRNA KCNQ1OT1 can target and regulate the miR-124-3p/HMGB1 axis, thereby promoting proliferation and fibrosis and inhibiting apoptosis in high-glucose-induced glomerular mesangial cells. The present study showed that serum miR-124-3p levels were lower in the DN group than in the control group, lower in the progression group than in the non-progression group, and lower in the poor-prognosis group than in the good-prognosis group. These findings indicate that serum miR-124-3p levels may be associated with the occurrence and development of DN, and that DN progression is accompanied by changes in serum miR-124-3p levels. miR-124-3p may participate in DN progression through mechanisms related to apoptosis and inflammation [6].

Multivariate logistic regression analysis in this study showed that serum miR-93-5p and miR-124-3p levels were factors associated with short-term progression of albuminuria and poor prognosis in patients with DN. The lower the serum levels of miR-93-5p and miR-124-3p, the higher the risk of short-term progression of albuminuria and poor prognosis. ROC curve analysis showed that serum miR-93-5p and miR-124-3p levels alone had moderate predictive value for poor prognosis in patients with DN, with AUCs of 0.856 and 0.852, respectively. However, the combined detection of the two miRNAs showed better predictive value for poor prognosis in patients with DN, with an AUC of 0.945.

In conclusion, serum miR-93-5p and miR-124-3p levels in patients with DN are associated with short-term progression of albuminuria and poor prognosis. Combined detection of these two miRNAs has good predictive value for poor prognosis in patients with DN. The limitations of this study include its small sample size and limited generalizability. Future studies with larger patient cohorts are needed to further validate these findings.

Conflict of Interest None

Reference

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· 论 著 ·

血清 miR-93-5p 及 miR-124-3p 水平与糖尿病肾病 患者白蛋白尿短期进展和预后的关系

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摘要: **目的** 分析糖尿病肾病(DN)患者血清微小RNA(miR)-93-5p 和 miR-124-3p 表达水平,并探究二者水平变化与 DN 患者白蛋白尿短期进展及预后的关系。**方法** 回顾性选取哈尔滨市第一医院 2021 年 1 月至 2023 年 8 月收治的 116 例 DN 患者作为 DN 组,同期选择 120 例健康体检者作为对照组。依据白蛋白尿短期进展情况将 DN 患者分为进展组(32 例)及未进展组(84 例)。根据 1 年随访患者是否发生终末期肾病、肾功能衰竭或尿毒症,分为预后不良组(41 例)及预后良好组(75 例)。采用荧光定量聚合酶链式反应检测受检者血清 miR-93-5p 和 miR-124-3p 水平,多因素 logistic 回归分析 DN 患者白蛋白尿短期进展及预后不良的影响因素,采用受试者工作特征(ROC)曲线分析血清 miR-93-5p 和 miR-124-3p 水平单独及联合检测对 DN 患者预后不良的预测价值。**结果** 血清 miR-93-5p 和 miR-124-3p 水平在 DN 组低于对照组($P<0.05$),在进展组低于未进展组($P<0.05$),在预后不良组低于预后良好组($P<0.05$)。多因素 logistic 回归分析显示血清 miR-93-5p 和 miR-124-3p 水平是 DN 患者白蛋白尿短期进展及预后不良的独立影响因素($P<0.05$),二者联合预测 DN 患者预后不良的曲线下面积(AUC)(0.945)高于 miR-93-5p (AUC=0.856)、miR-124-3p (AUC=0.852)单独预测,差异有统计学意义($Z=2.504, P=0.012; Z=2.551, P=0.011$)。**结论** DN 患者血清 miR-93-5p 和 miR-124-3p 水平与白蛋白尿短期进展及预后相关,二者联合检测对 DN 患者不良预后具有较好的预测价值。

关键词: 糖尿病肾病; 微小 RNA-93-5p; 微小 RNA-124-3p; 白蛋白尿; 短期进展

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Relationship of serum miR-93-5p and miR-124-3p levels with short-term progression of albuminuria and prognosis in patients with diabetic nephropathy

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Abstract: Objective To measure the expression levels of serum micro RNA (miR) -93-5p and miR-124-3p in patients with diabetic nephropathy (DN), and to explore the relationship of their changes with the short-term progression and prognosis of albuminuria. **Methods** A total of 116 DN patients admitted to Harbin First Hospital between January 2021 and August 2023 were retrospectively selected as DN group, and 120 healthy individuals in the same period were selected as control group. Patients with DN were categorized into a progressive group (32 cases) and a non-progressive group (84 cases) based on the short-term progression of albuminuria. And patients with DN were divided into poor prognosis group (41 cases) and good prognosis group (75 cases) according to whether patients developed end-stage renal disease, renal failure and uremia after one-year follow-up. Fluorescence quantitative polymerase chain reaction was used to detect the levels of serum miR-93-5p and miR-124-3p in the subjects. Multivariate logistic regression



analysis was conducted to identify the factors influencing short-term progression of albuminuria and poor prognosis in DN patients. The predictive value of serum miR-93-5p and miR-124-3p levels, individually and combined, for poor prognosis in DN patients was analyzed using receiver operating characteristic (ROC) curve. **Results** The serum levels of miR-93-5p and miR-124-3p were lower in DN group compared to control group ($P<0.05$), were lower in progression group compared to non-progression group ($P<0.05$), and were lower in poor prognosis group than those in good prognosis group ($P<0.05$). Multivariate logistic regression analysis showed that serum levels of miR-93-5p and miR-124-3p were independent factors affecting the short-term progression of albuminuria and poor prognosis in DN patients ($P<0.05$). The combined prediction of poor prognosis in DN patients by these two miRNAs had a higher area under curve (0.945) than that of miR-93-5p (0.856) or miR-124-3p alone (0.852), with statistically significant differences ($Z=2.504$, $P=0.012$; $Z=2.551$, $P=0.011$). **Conclusion** The serum miR-93-5p and miR-124-3p in DN patients are associated with short-term progression and prognosis of albuminuria. The combined testing has a good predictive value for poor prognosis in DN patients.

Keywords: Diabetic nephropathy; MicroRNA-93-5p; MicroRNA-124-3p; Albuminuria; Short-term progression

糖尿病肾病(diabetic nephropathy, DN)是糖尿病主要的微血管并发症,病理生理过程涉及趋化因子、促炎细胞因子、黏附分子等多种生物活性物质的异常表达^[1]。DN具体病程包括无白蛋白尿期、微量白蛋白尿期及大量蛋白尿期^[2]。尿白蛋白增加是肾小球损伤的重要标志^[2]。探究与白蛋白尿短期进展有关的血清标志物有助于辅助临床早期展开治疗。微小RNA(microRNA, miR)-93-5p能够通过不同信号通路参与DN的病理过程^[3]。提高miR-93-5p水平能够改善高葡萄糖诱导的肾小球系膜细胞增殖、纤维化及炎症^[4]。研究显示,高糖及高脂条件下,miR-124-3p水平下调能够诱导肾小管上皮细胞异常导致线粒体功能障碍,促进DN的发展^[5]。miR-124-3p能够通过氧化应激、自噬、铁死亡及炎症等途径参与各种肾脏疾病的发展过程,包括DN、急性肾损伤及狼疮性肾炎^[6]。现阶段,血清miR-93-5p和miR-124-3p水平与DN患者白蛋白尿短期进展及预后的关系尚不清楚,本研究就此展开探讨。

1 对象与方法

1.1 研究对象 回顾性选取哈尔滨市第一医院肾内科2021年1月—2023年8月收治的116例DN患者作为DN组。(1)纳入标准:①诊断符合《2型糖尿病分级诊疗与质量管理专家共识》^[7]中2型糖尿病的标准;②诊断符合《糖尿病肾脏疾病临床诊疗中

国指南》^[8]中有关DN的标准。(2)排除标准:①合并严重感染、免疫或血液系统疾病;②伴随肾炎;③近3个月服用过影响肾功能的药物。DN组年龄(55.76 ± 5.42)岁,女59例,男57例。同期选择120例健康体检者作为对照组,年龄(56.03 ± 5.47)岁,女64例,男56例。两组性别、年龄差异无统计学意义($P>0.05$)。本研究经哈尔滨市第一医院医学伦理委员会的批准(编号:伦审2024-047),受试者均签署同意书。

1.2 方法

1.2.1 一般资料 入组后从患者病历中获取临床资料,包括年龄、性别、身体质量指数(body mass index, BMI)、糖尿病病程、合并症[高血压、高脂血症、冠状动脉粥样硬化性心脏病(冠心病)]、吸烟史、饮酒史、家族遗传史等。

1.2.2 血清指标检测 入院后治疗前采集DN患者空腹静脉血4 mL,对照组于体检当天采集,室温静置30~60 min,2 500 r/min下离心10 min(离心半径为10 cm),取上清液低温保存待用。取血清提取RNA后反转录为cDNA,采用荧光定量聚合酶链式反应(quantitative polymerase chain reaction, qPCR)检测血清miR-93-5p、miR-124-3p水平,相关内参为U6,引物序列^[9-10]见表1,引物合成由武汉金开瑞生物工程完成。反应体系为5 μ L PCR master mix, ddH₂O 3 μ L,引物1 μ L(正向、反向各0.5 μ L), cDNA 1 μ L。反应程序为95 $^{\circ}$ C 52 s, 95 $^{\circ}$ C 37 s; 56 $^{\circ}$ C 30 s; 72 $^{\circ}$ C 10 s, 共计35个循环。

表1 血清miR-93-5p、miR-124-3p及U6的引物序列

Tab.1 Primer sequences for serum miR-93-5p, miR-124-3p, and U6

引物名称	正向序列 5'→3'	反向序列 5'→3'
miR-93-5p	ACA CTC CAG CTG GGT CCT GTA CTG ACG TGC CC	CTC AAC TGG TGT CGT GGA
miR-124-3p	TCT TTA AGG CAC GCG GTG	TAT GGT TTT GAC GAC TGT GTG AT
U6	GCT TCG GCA GCA CAT ATA CTA AAA T	CGC TTC ACG AAT TTG CGT GTG TCA T

1.2.3 白蛋白尿短期进展评估 对患者进行动态随访监测,于入组时及6个月后分别收集24 h尿白蛋白及血清肌酐(serum creatinine, SCr)检测数据,依据白蛋白尿短期进展的判定标准^[11]将患者分为进展组及未进展组。首次检测24 h尿白蛋白水平范围为30~300 mg,二次检测时24 h尿白蛋白水平>300 mg;或首次检测时24 h尿白蛋白水平>300 mg,二次检测SCr水平是首次检测的2倍,满足任一上述条件即可诊断为白蛋白尿短期进展。

1.2.4 随访及预后评估 通过门诊复查及电话随访进行为期1年的观察,截止时间为2024年8月,根据随访终点事件是否发生终末期肾病、肾功能衰竭或尿毒症,将患者划分为预后不良组及预后良好组。

1.3 统计学方法 使用SPSS 24.0软件处理数据。计数资料表示为例(%),比较采用 χ^2 检验。符合正态分布的计量资料表示为 $\bar{x}\pm s$,两组比较采用独立样本 t 检验,方差不齐时采用 t 检验校正法。采用多因素logistic回归分析DN患者白蛋白尿短期进展及预后不良的影响因素,绘制受试者工作特征(receiver operating characteristic,ROC)曲线分析血清miR-93-5p、miR-124-3p水平单独及二者联合对DN患者预后不良的预测价值,曲线下面积(area under curve, AUC)比较采用DeLong检验。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 DN组与对照组血清miR-93-5p、miR-124-3p水平比较 DN组血清miR-93-5p水平(0.66 ± 0.11 vs 1.01 ± 0.15 , $P<0.01$)、miR-124-3p水平(0.80 ± 0.12 vs 1.02 ± 0.13 , $P<0.01$)低于对照组。

2.2 进展组及未进展组一般资料及血清miR-93-5p、miR-124-3p水平比较 116例DN患者中,32例出现白蛋白尿短期进展(进展组),84例未出现白蛋白尿短期进展(未进展组)。进展组及未进展组一般资料比较差异无统计学意义($P>0.05$),进展组血清miR-93-5p、miR-124-3p水平低于未进展组($P<0.05$)。见表2。

2.3 多因素logistic回归分析DN患者白蛋白尿短期进展的影响因素分析 以DN患者白蛋白尿短期进展为因变量(进展=1,未进展=0),以血清miR-93-5p、miR-124-3p水平作为自变量(原值代入),进行多因素logistic分析结果显示,二者均是DN患者白蛋白尿短期进展的影响因素($P<0.05$)。见表3。

2.4 预后不良组和预后良好组的一般资料及血清miR-93-5p、miR-124-3p水平比较 预后不良组和预后良好组一般资料比较差异无统计学意义($P>0.05$),预后不良组血清miR-93-5p、miR-124-3p水平低于预后良好组($P<0.05$)。见表4。

2.5 多因素logistic回归分析DN患者预后不良的影响因素 以DN患者预后不良作为因变量(预后不良=1,预后良好=0),以单因素分析有统计学意义的血清miR-93-5p、miR-124-3p水平作为自变量(原值代入),多因素分析结果显示,二者均是DN患者预后不良的影响因素($P<0.05$)。见表5。

2.6 血清miR-93-5p、miR-124-3p水平对DN患者预后不良的预测价值 血清miR-93-5p、miR-124-3p联合检测DN患者预后不良的AUC高于miR-93-5p单独预测($Z=2.504$, $P=0.012$),高于miR-124-3p单独预测($Z=2.551$, $P=0.011$)。见表6、图1。

表2 进展组及未进展组一般资料及血清miR-93-5p、miR-124-3p水平比较 [例(%)]

Tab.2 Comparison of general data and serum levels of miR-93-5p and miR-124-3p between progression group and non-progression group [case(%)]

项目	进展组 (n=32)	未进展组 (n=84)	χ^2/t 值	P值
年龄				
≥55岁	12(37.50)	25(29.76)	0.639	0.424
<55岁	20(62.50)	59(70.24)		
性别				
男	12(37.50)	45(53.57)	2.395	0.122
女	20(62.50)	39(46.43)		
BMI(kg/m ² , $\bar{x}\pm s$)	22.88±2.45	22.35±2.23	1.113	0.268
糖尿病病程				
≥10年	17(53.13)	34(40.48)	1.505	0.220
<10年	15(46.88)	50(59.52)		
高血压	14(43.75)	30(35.71)	0.636	0.425
高脂血症	17(53.13)	36(42.86)	0.985	0.321
冠心病	16(50.00)	38(45.24)	0.211	0.646
吸烟史	19(59.38)	36(42.86)	2.536	0.111
饮酒史	21(65.63)	43(51.19)	1.952	0.162
家族遗传史	17(53.13)	40(47.62)	0.281	0.596
miR-93-5p($\bar{x}\pm s$)	0.52±0.09	0.72±0.12	8.547	<0.001
miR-124-3p($\bar{x}\pm s$)	0.69±0.10	0.84±0.13	5.891	<0.001

表3 DN患者白蛋白尿短期进展的影响因素分析

Tab.3 Analysis of factors influencing short-term progression of albuminuria in patients with DN

变量	β	SE	Wald χ^2	P值	OR值	95%CI
miR-93-5p	-1.168	0.237	24.286	<0.001	0.311	0.195~0.495
miR-124-3p	-0.901	0.337	7.154	0.007	0.406	0.210~0.786

表4 预后不良组和预后良好组一般资料及血清 miR-93-5p、miR-124-3p 水平比较 [例(%)]**Tab.4** Comparison of general data and serum miR-93 and miR-124 levels between the poor-prognosis group and the good-prognosis group [case (%)]

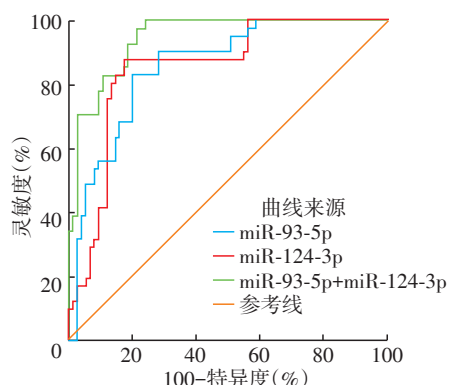
项目	预后不良组 (n=41)	预后良好组 (n=75)	χ^2 值	P 值
年龄				
≥55 岁	14(34.15)	23(30.67)	0.148	0.701
<55 岁	27(65.85)	52(69.33)		
性别				
男	18(43.90)	39(52.00)	0.695	0.404
女	23(56.10)	36(48.00)		
BMI(kg/m ²)	22.75±2.38	22.36±2.24	0.877	0.382
糖尿病病程				
≥10 年	22(53.66)	29(38.67)	2.418	0.120
<10 年	19(46.34)	46(61.33)		
高血压	20(48.78)	24(32.00)	3.170	0.075
高脂血症	22(53.66)	31(41.33)	1.623	0.203
冠心病	24(56.10)	30(40.00)	2.768	0.096
吸烟史	23(56.10)	32(42.67)	1.918	0.166
饮酒史	27(65.85)	37(49.33)	2.925	0.087
家族遗传史	21(51.22)	36(48.00)	0.110	0.740
miR-93-5p($\bar{x}\pm s$)	0.57±0.08	0.71±0.12	7.504	<0.001
miR-124-3p($\bar{x}\pm s$)	0.70±0.11	0.86±0.13	6.678	<0.001

表5 DN 患者预后不良的影响因素分析**Tab.5** Analysis of factors influencing poor prognosis in patients with DN

变量	β	SE	Wald χ^2	P 值	OR 值	95%CI
miR-93-5p	-1.115	0.301	13.716	<0.001	0.328	0.182~0.592
miR-124-3p	-1.149	0.237	23.498	<0.001	0.317	0.199~0.504

表6 血清 miR-93-5p、miR-124-3p 水平对 DN 患者预后不良的预测价值**Tab.6** Predictive value of serum miR-93-5p and miR-124-3p levels for poor prognosis in patients with DN

指标	AUC	截断值	灵敏度 (%)	特异度 (%)	95%CI
miR-93-5p	0.856	0.669	82.93	80.00	0.779~0.914
miR-124-3p	0.852	0.795	87.80	82.67	0.774~0.911
miR-93-5p+miR-124-3p	0.945	—	97.56	78.67	0.886~0.979

**图1** 血清 miR-93-5p、miR-124-3p 水平单独及联合预测 DN 患者预后不良的 ROC 曲线**Fig.1** ROC curve of serum miR-93-5p and miR-124-3p levels alone and in combination for predicting poor prognosis in patients with DN

3 讨论

糖尿病并发症中的 DN, 对患者的生命安全产生重大威胁^[1]。现阶段, 糖尿病的发病人数逐渐增加, DN 的发生人数也随之增加^[12]。DN 的病理机制较为复杂, 其典型进展被描述为蛋白尿和肾小球滤过率降低^[13], 临床病理特征包括系膜扩张、肾小管间质纤维化及肾小球基底膜增厚。微量白蛋白尿是 DN 发展的首要症状, 微量白蛋白尿表现为间歇性改变, 随着患者病情加重, 高血糖损伤肾小球滤过膜, 滤过膜孔径增加, 当血浆白蛋白滤过率高于肾小球吸收能力时, 患者进入显性白蛋白尿期^[14]。反映肾功能恶化的最佳预测指标是白蛋白尿, 因此, 探究与白蛋白尿短期进展相关的血清标志物十分重要^[15]。DN 的病情进展较快, 通常还伴随其他并发症, 肾功能恶化速度较快, 患者预后效果较差, 早期预测 DN 患者不良预后的发生风险有助于临床及时实施干预治疗, 可有效改善 DN 患者的预后情况及生存率^[8]。本研究对 DN 患者血清 miR-93-5p、miR-124-3p 水平与 DN 患者白蛋白尿短期进展及预后的关系进行检测分析, 旨在辅助临床评估患者预后。

miR-93-5p 在 DN 的发生发展进程中扮演关键调控角色, 可通过靶向调控下游靶基因表达等多种作用机制, 参与糖尿病肾病的病理生理过程^[16]。顾勇等^[17]研究显示, miR-93-5p 可阻碍高血糖诱导的足细胞炎性因子的分泌及凋亡, 其作用机制与 miR-93-5p 靶向双特异性磷酸酶 8 有关。本研究中 DN 组较对照组血清 miR-93-5p 水平降低, 与 Wang 等^[4]研究结果一致, 证实 miR-93-5p 水平变化可能与 DN 的发生有关。依据白蛋白尿短期进展分组分析发现, 进展组较未进展组血清 miR-93-5p 水平降低, 提示 miR-93-5p 可能参与 DN 患者白蛋白尿短期进展过程。分析预后发现, 预后不良组较预后良好组血清 miR-93-5p 水平低, 表明 miR-93-5p 水平与预后有关, 其参与 DN 发生与发展过程的机制可能是低 miR-93-5p 水平对炎症因子释放及氧化应激的抑制作用减弱, 患者预后不良的发生风险增加^[18]。

miR-124-3p 可能通过促进肾脏纤维化及慢性炎症反应等途径参与 DN 的发生与发展过程, 其水平下调与 DN 中的慢性炎症反应及肾脏纤维化有关^[5]。长链非编码 RNA KCNQ10T1 敲低后通过促进肾纤维化中 miR-124-3p 的表达起到抗纤维化的效果, 是潜在的治疗肾纤维化的靶点^[19]。路华等^[20]研究也发现, 长链非编码 RNA KCNQ10T1 可靶向调控 miR-124-3p

水平降低,促进高糖条件下肾小球系膜细胞的增殖及细胞纤维化,抑制凋亡。本研究结果显示,在血清miR-124-3p水平比较中,DN组低于对照组,进展组低于未进展组,预后不良组低于预后良好组,这反映了血清miR-124-3p水平可能与DN的发生及发展有关,表明DN的发生与发展过程伴随血清miR-124-3p水平变化,miR-124-3p参与DN发生与发展过程的机制可能与细胞凋亡及炎症有关^[6]。

本研究多因素 logistic 回归分析发现,血清miR-93-5p、miR-124-3p水平是DN患者白蛋白尿短期进展及预后不良的影响因素,患者血清miR-93-5p、miR-124-3p水平越低,发生白蛋白尿短期进展及预后不良的风险越高。ROC曲线分析发现,血清miR-93-5p、miR-124-3p水平的单独预测DN患者预后不良的价值一般(AUC分别为0.856和0.852),但二者联合对DN患者发生预后不良的预测价值较好(AUC=0.945)。

综上所述,DN患者血清miR-93-5p、miR-124-3p水平与患者白蛋白尿短期进展及预后不良相关,联合检测对DN患者发生不良预后具有较好的预测价值。本研究的不足之处在于样本量少、研究结果普适性不强,后续将纳入更多患者对本研究结果进行分析验证。

利益冲突 无

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