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ORIGINAL RESEARCH

Diagnostic Value of Serum miR-17-5p in Type 2 Diabetes Mellitus and Its Predictive Value for Chronic Complications

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Purpose: This study aims to explore the clinical significance of miR-17-5p in T2DM and its chronic complications.

Patients and Methods: A total of 100 patients with T2DM and 90 healthy controls were included. The expression of miR-17-5p was detected by reverse transcription-polymerase chain reaction. A receiver operating characteristic curve was plotted to evaluate the diagnostic value of miR-17-5p for T2DM. Pearson correlation analysis was used to explore the correlation between miR-17-5p and blood glucose indicators in T2DM patients. The Kaplan-Meier curve and multivariate Cox regression analysis were employed to analyze the factors influencing chronic complications. Liposome-mediated transfection technology was used to transfect miR-17-5p mimics and inhibitors into endothelial progenitor cells (EPCs) respectively, to achieve overexpression and knockdown of miR-17-5p in cells. On this basis, we further investigate the potential molecular mechanism by which miR-17-5p is involved in the occurrence and development of chronic complications inT2DM.

Results: Serum miR-17-5p was significantly downregulated in T2DM patients (vs healthy controls, P<0.001). The AUC for distinguishing T2DM patients from healthy individuals was 0.932. The expression of this miRNA was significantly negatively correlated with FBG (r=−0.718) and HbA1c (r=−0.695) (P<0.001). Follow-up showed that low expression of miR-17-5p was closely associated with T2DM chronic complications (complication group vs non-complication group, P<0.001), with an AUC of 0.866 for distinguishing the presence from the absence of complications. Kaplan-Meier analysis indicated that individuals with low miR-17-5p expression had a higher risk of complications (Log-rank P=0.009). Mechanistically, miR-17-5p targets FBXO48 and affects the functions of EPCs.

Conclusion: The expression of miR-17-5p is reduced in T2DM. It influences the functions of EPCs by targeting *FBXO48*, and may be involved in the occurrence and development of chronic complications of T2DM.

Keywords: T2DM, chronic complications, miR-17-5p, EPCs

Introduction

Type 2 diabetes mellitus (T2DM) is a common endocrine and metabolic disorder in clinical practice.[1] According to statistics, the prevalence of diabetes is constantly increasing worldwide.[2] Diabetes predisposes individuals to a range of complications affecting both large and small blood vessels throughout the body, such as cardiovascular diseases, diabetic nephropathy, retinopathy, and neuropathy.[3,4] These vascular complications are major drivers of disability and mortality in T2DM patients, significantly impairing their quality of life and overall health.[5] Therefore, the early detection of vascular lesions is imperative for the effective management of T2DM. Nonetheless, the search for reliable predictive indicators remains a significant challenge in clinical practice.

In recent years, microRNAs (miRNAs) have garnered significant attention within the scientific community.[6] Numerous studies have elucidated the intricate relationship between miRNAs and the onset and progression of diabetes, highlighting their crucial role in regulating physiological processes associated with blood glucose levels and metabolic functions.[7,8] Studies on miRNAs not only deepen our understanding of the genetic mechanisms underlying T2DM but

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also provide valuable insights for its early diagnosis, therapeutic development, and prognostic evaluation.[9] miR-335-5p has been implicated as a potential therapeutic target for T2DM.[10] Serum miR-7 is a potential biomarker for T2DM and its microvascular complications.[11] Under different research backgrounds and disease models, the expression status of miR-17-5p shows significant differences. In diabetes-related studies, multiple pieces of literature have pointed out that its expression trend is downregulated. For example, miR-17-5p in the peripheral blood of diabetic patients is downregulated.[12] miR-17-5p expression is also downregulated in gestational diabetes mellitus, and it can alleviate the inflammatory response and apoptosis of trophoblasts under high glucose conditions.[13] Studies have shown that diabetes and a high-glucose environment can downregulate the expression of miR-17-5p,[14] further implying a close association with the pathological processes of diabetes. In addition, Pan et al found that in a diabetic hindlimb ischemia model, enrichment of miR-17-5p can enhance the vascular protective effect of exosomes derived from EPCs,[12] suggesting a potential regulatory role of miR-17-5p in diabetic vascular lesions.

Although existing studies have revealed the potential role of miR-17-5p in diabetes, its specific expression and potential functions in patients with T2DM remain unclear. Therefore, this study aims to explore the clinical significance of miR-17-5p in T2DM and its chronic complications, providing new insights for the diagnosis and treatment of T2DM.

Materials and Methods

Research Subjects

The study included 100 patients with T2DM diagnosed with T2DM who received care at the Affiliated Hospital of Jiangnan University from January 2018 to January 2020. Meanwhile, the control group comprised 90 healthy individuals who underwent routine health check-ups at the same institution during the corresponding period.

Inclusion criteria: Adherence to the diagnostic criteria for T2DM stipulated in Chinese Guidelines for the Prevention and Treatment of T2DM (2020 Edition)";[15] Possession of complete and authentic medical records. Exclusion criteria: Type 1 diabetes or other types of diabetes; those with definite coagulation dysfunction, specifically including congenital coagulation factor deficiency, acquired coagulation abnormalities, and abnormalities in platelet count and function; those with acute diabetic complications, including diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome, lactic acidosis, and severe hypoglycemic coma; patients with mental disorders; coexisting malignant tumors, other endocrine systems disorders, immune systems disorders, blood systems disorders, severe infections, etc.

Approval was obtained from the ethics committee of Affiliated Hospital of Jiangnan University. The procedures used in this study adhere to the tenets of the Declaration of Helsinki, and all patients signed informed consent forms.

Data Collection

All pertinent basic information and biochemical indicators for each patient were meticulously collected. This included age, gender, body mass index (BMI), any underlying medical conditions, as well as key metabolic parameters such as fasting blood glucose (FBG), hemoglobin A1c (HbA1c), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Prior to the initiation of treatment, venous blood was drawn from the patients, followed by centrifugation to obtain serum for subsequent analysis.

Real-Time Quantitative PCR

Total RNA was extracted utilizing the Trizol extraction kit (Invitrogen, USA), and the concentration and purity of the RNA were assessed with a NanoDrop2000 spectrophotometer. After qualification, total RNA was reverse-transcribed into cDNA using the Taqman miRNA reverse transcription kit (YaJi mall, Shanghai). Quantitative RT-PCR was conducted using the ABI 7500 Fast Real-Time PCR System, with each sample tested a minimum of three times and each experiment replicated three times. U6 was used as the endogenous control for normalization. A melting curve analysis was performed post-amplification, and the relative expression level of serum miR-17-5p was determined using the $2^{-\Delta\Delta Ct}$ method based on the corresponding Ct values.

Nursing Interventions

All T2DM patients received standardized basic nursing interventions, including routine blood glucose monitoring and dietary guidance, standardized medication management, basic condition monitoring, and follow-up management. The aim was to reduce potential confounding effects of drastic blood glucose fluctuations or treatment differences on the assessment of miR-17-5p expression levels and chronic complications through unified intervention measures, so as to ensure the reliability of the research results.

Follow-Up

All patients were monitored primarily through telephone consultations and outpatient visits. Follow-up commenced at the time of T2DM diagnosis and continued until the onset of chronic complications or the completion of a five-year follow-up period. T2DM complications affect multiple important systems, including macrovascular complications (such as coronary heart disease, stroke and peripheral artery disease), microvascular complications (diabetic nephropathy, diabetic retinopathy, diabetic neuropathy), and other complications such as diabetic foot and diabetic skin lesions.

Cell Culture and Transfection

EPCs were acquired from SAIOS (Wuhan) and subsequently cultured in EGM-2 complete medium supplemented with 10% fetal bovine serum (FBS) within a 5% CO_2 incubator maintained at 37°C. Cells in the logarithmic growth phase were selected for the transfection process. The transfection was performed utilizing Lipofectamine™ 3000 (Invitrogen, USA). Subsequent experiments were executed 48 hours post-transfection. The designated experimental groups for cell transfection included: a control group (no transfection), a mimic NC group (transfected with a mimic negative control), a miR-17-5p mimic group (transfected with the miR-17-5p mimic), an inh-NC group (transfected with an inhibitor negative control), and an inh-miR-17-5p group (transfected with the miR-17-5p inhibitor).

CCK-8 Assay to Detect Cell Proliferation Ability

Transfected cells in each group were harvested, digested, and inoculated into 24-well plates (2.5×10^4 cells/well). The culture plates were placed in a CO_2 incubator at 37°C with 5% CO_2 for incubation for 24, 48 and 72 hours. After incubation, 10 μL of CCK-8 solution was added to each well, and the plates were returned to the incubator for 1 hour. Absorbance was measured at 450 nm using an ELISA spectrophotometer.

Annexin V/PI Flowcytometric Detection of Cells Apoptotic

Transfected cells from each group were collected and digested with 0.125% trypsin. Cells were centrifuged, washed once with phosphate-buffered saline (PBS), recentrifuged, and the supernatant was discarded. Cell pellets were resuspended in 1x Annexin binding buffer to a final concentration of 1×10^6 cells/ mL. 5 μL Alexa Fluor 488 Annexin V and 1 μL 100 μg/mL propidium iodide (PI) were added to 100 μL of cell suspension, and the mixture was incubated at room temperature in the dark for 15 minutes. After incubation, Annexin binding buffer was added to each sample and mixed thoroughly. Flow cytometry was used to detect the cells and calculate the apoptosis rate.

Dual-Luciferase Reporter Gene Assay

The TargetScan database indicates that miR-17-5p possesses binding sites within the *FBXO48* nucleotide sequence. The fragment containing the *FBXO48*-3'UTR sequence and the binding site of miR-17-5p was amplified by PCR technology. This amplified fragment was subsequently inserted into the luciferase pGL4 vector to establish the wild-type construct of *FBXO48* (*FBXO48*-wt). Furthermore, through the application of gene mutation techniques, specific binding site sequences were mutated to generate the mutant construct (*FBXO48*-mut). For the experimental procedure, Lipofectamine™ 3000 was employed to co-transfect the *FBXO48*-wt and *FBXO48*-mut constructs along with miR-17-5p mimic and inh-miR-17-5p into EPCs, respectively. Following a 48-hour transfection period, the cells were washed with PBS, and RIPA lysis buffer (250 μL) was added. Cells were incubated in a shaking incubator at room temperature for 15 minutes to facilitate lysis. The lysate was collected, and 50 mL of Luciferase Detection Reagent II was added to

measure the fluorescence intensity A using an automated luciferase detector. Subsequently, Stop & Glo was introduced to determine the fluorescence intensity B. The relative luciferase activity was then calculated as the ratio of A to B.

Statistical Methods

G*Power (version 3.1.9.7) was used to calculate and determine the sample size, with α set at 0.05 (two-tailed test) and test power (1-β) set at 0.85. Data analysis was conducted utilizing SPSS version 26.0 statistical software. Measurement data were presented as the mean ± standard deviation (mean ± SD), with comparisons performed via analysis of variance (ANOVA). For pairwise comparisons, the LSD-*t* test was employed. Count data were expressed as proportions of their respective components, and comparisons were executed using the χ^2 test. $P < 0.05$ was set to indicate statistical significance.

Results

Comparison of the Clinical Characteristics of the Subjects

Clinical data and biochemical test results for both groups are presented in Table 1. There were no statistically significant differences in gender, age, BMI, history of hypertension, TC and LDL-C levels between the two groups ($P > 0.05$). Notably, TG, FBG, and HbA1c (%) in the T2DM group were markedly elevated compared to the control group, whereas the HDL-C levels were substantially lower in the T2DM group ($P < 0.05$).

Expression of miR-17-5p in T2DM and Its Correlation with Blood Glucose Indicators

RT-qPCR results revealed a significant decrease in serum miR-17-5p levels in T2DM patients compared to the control group ($P < 0.001$) (Figure 1A). The ROC curve was constructed to assess the diagnostic utility of miR-17-5p in identifying T2DM. The analysis demonstrated an area under the curve (AUC) of 0.932 (95% CI = 0.898–0.966), with sensitivity and specificity rates of 92% and 81.1%, respectively (Figure 1B). Pearson correlation analysis revealed a significant negative correlation between serum miR-17-5p levels and both FBG ($r = -0.718$) and HbA1c (%) percentages ($r = -0.695$) ($P < 0.001$) (Figure 1D–E).

Table 1 Clinical Characteristics of the Study Participants

Variable	Control (n=90)	T2DM (n=100)	*P* value
Age (years)	51.74±3.46	51.91±3.75	0.753
Gender (male/female)	43/47	55/45	0.323
BMI (kg/m^2)	23.95±1.23	24.11±1.15	0.366
Hypertension (yes/no)	42/48	54/46	0.315
TC (mmol/L)	4.55±0.66	4.72±0.58	0.071
TG (mmol/L)	1.68±0.12	2.03±0.24	<0.001***
HDL-C (mmol/L)	1.35±0.19	1.28±0.17	0.004**
LDL-C (mmol/L)	2.40±0.23	2.44±0.20	0.152
FBG (mmol/L)	4.96±0.57	7.76±0.52	<0.001***
HbA1c (%)	4.79±0.56	8.49±0.82o	<0.001***

Note: **P <0.01, ***P<0.001.

Abbreviations: T2DM, Type 2 diabetes mellitus; BMI, body mass index; TC, Serum total cholesterol; TG, Triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, *low-density lipoprotein* cholesterol; FBG, fasting blood glucose; HbA1c (%), glycosylated hemoglobin.

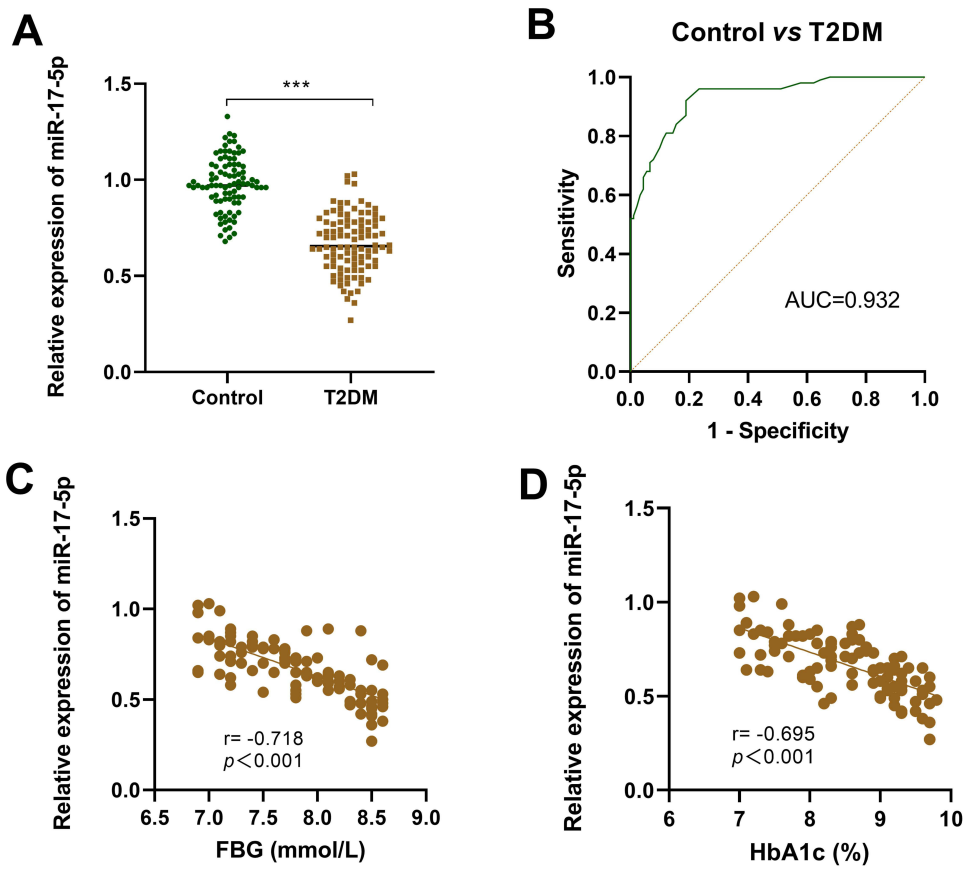

Figure 1 Expression of miR-17-5p in T2DM and Its Correlation with Blood Glucose Indicators. The serum miR-17-5p level in T2DM patients was significantly decreased (P<0.001) (**A**). ROC curves for the assessment of the diagnostic value of miR-17-5p in T2DM (**B**). The serum miR-17-5p level was significantly negatively correlated with both FBG and HbA1 (%) (**C** and **D**). ***P<0.001.

Relationship Between miR-17-5p Expression and Clinical Characteristics of T2DM

The 100 patients were categorized into two groups based on the median expression level of miR-17-5p in T2DM individuals: a low miR-17-5p level group (n = 52) and a high miR-17-5p level group (n = 48). Low miR-17-5p expression was closely associated with TG, FBG, and HbA1c in T2DM patients (P < 0.05) (Table 2).

Table 2 The Relationship Between miR-17-5p Expression and Clinical Characteristics of T2DM

Variable	miR-17-5p Expression Level		*P* value
	Low (n=52)	High (n=48)	
TC (mmol/L)	4.64±0.58	4.80±0.57	0.159
TG (mmol/L)	1.99±0.23	2.08±0.24	0.045*
HDL-C (mmol/L)	1.30±0.18	1.26±0.16	0.201
LDL-C (mmol/L)	2.41±0.19	2.48±0.20	0.072
FBG (mmol/L)	7.90±0.51	7.62±0.51	0.008**
HbA1c (%)	8.68±0.83	8.27±0.76	0.013*

Note: *P <0.05, **P <0.01.

Abbreviations: TC, Serum total cholesterol; TG, Triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c (%), glycosylated hemoglobin.

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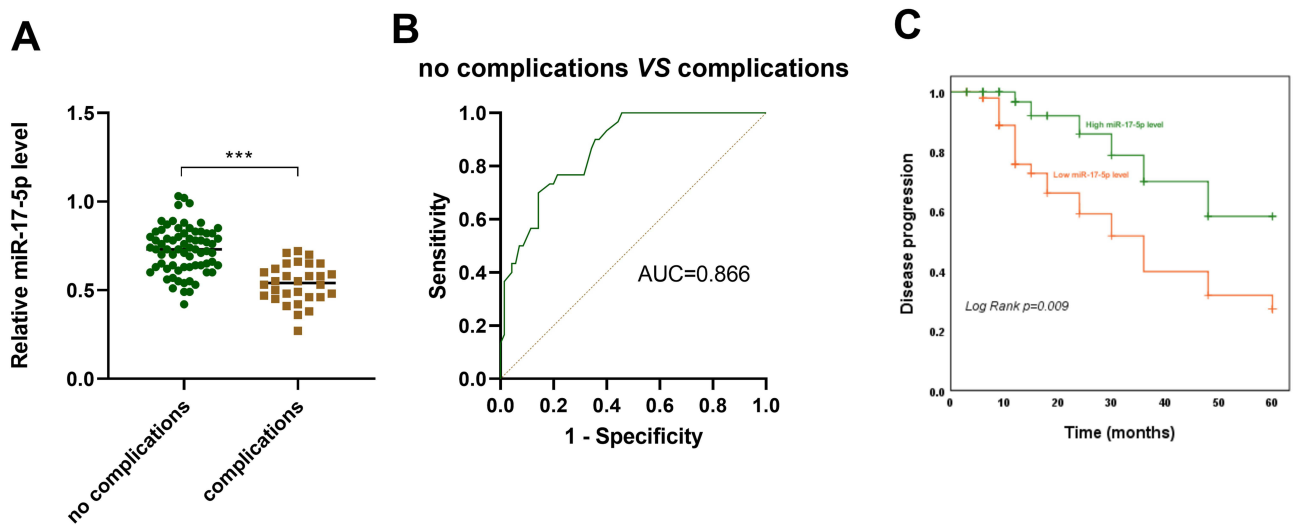

Figure 2 Correlation between miR-17-5p and Chronic Complications of T2DM. The expression level of miR-17-5p in the T2DM with chronic complications group was significantly lower than that in the non-complication group (P < 0.001) (**A**). ROC curve of miR-17-5p for distinguishing T2DM patients with or without chronic complications (**B**). Kaplan-Meier curve showing the cumulative incidence of chronic complications in T2DM patients with low vs high miR-17-5p expression levels (**C**). *** P<0.001.

Association of miR-17-5p with Chronic Complications of T2DM

Over a 5-year follow-up period, 30 T2DM patients developed chronic complications, comprising 23 instances of microvascular complications and 7 instances of macrovascular complications. RT-qPCR analysis revealed that miR-17-5p expression was significantly lower in patients with chronic complications than in those without (P < 0.001) (Figure 2A). Further ROC curve analysis results showed that miR-17-5p has a good ability to identify and distinguish individuals with T2DM without complications, with an area AUC of 0.866 (95% CI: 0.796–0.936), corresponding to a sensitivity of 76.7% and a specificity of 78.6% (Figure 2B). Kaplan-Meier analysis demonstrated that T2DM patients with low miR-17-5p levels had a significantly higher risk of developing chronic complications than those with high levels (Log-rank P=0.009) (Figure 2C).

Analysis of Risk Factors for Chronic Complications in T2DM Patients

Further analyze the influencing factors of the occurrence of chronic complications in patients with T2DM. A multivariate Cox analysis was performed with the dependent variable whether T2DM patients had chronic complications (0 for no complications, 1 for complications) and the independent variables serum miR-17-5p and clinical parameters. The results showed that miR-17-5p, hypertension, FBG level and HbA1c were related risk factors for the occurrence of chronic complications in patients with T2DM (P<0.05). While BMI might be a related factor for chronic complications of T2DM, it did not reach statistical significance (P>0.05) (Table 3).

Table 3 Multivariate Cox Analysis of Clinical Characteristics and Progression in T2DM Patients

Variable	HR	95% CI for HR		*P* value
		Lower	Upper	
miR-17-5p expression	0.254	0.081	0.794	0.018*
Age	1.612	0.660	3.938	0.295
Gender	0.859	0.352	2.093	0.738

(*Continued*)

Table 3 (Continued).

Variable	HR	95% CI for HR		*P* value
		Lower	Upper	
BMI	2.146	0.869	5.297	0.098
Hypertension	2.756	1.049	7.243	0.040*
TC	1.585	0.664	3.785	0.300
TG	1.570	0.666	3.703	0.303
HDL-C	0.551	0.228	1.331	0.185
LDL-C	2.143	0.828	5.543	0.116
FBG	3.351	1.319	8.517	0.011*
HbA1c (%)	2.647	1.164	6.020	0.020*

Note: *P <0.05.
Abbreviations: T2DM, Type 2 diabetes mellitus; BMI, body mass index; TC, Serum total cholesterol; TG, Triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c (%), glycosylated hemoglobin.

Effect of miR-17-5p on EPCs

To elucidate the potential mechanisms through which miR-17-5p may influence T2DM and its associated chronic complications, including microvascular and vascular complications, we established both overexpression and knockdown models of EPCs via transfection experiments. The transfection efficiency is illustrated in Figure 3A. CCK-8 assay results revealed that the overexpression of miR-17-5p significantly enhanced the proliferation of EPCs, whereas the knockdown of miR-17-5p led to a marked inhibition of cell proliferation (Figure 3B). Furthermore, apoptosis assay findings indicated that upregulation of miR-17-5p was associated with a reduction in the apoptosis rate of EPCs, while its knockdown resulted in an increased apoptosis rate (Figure 3C).

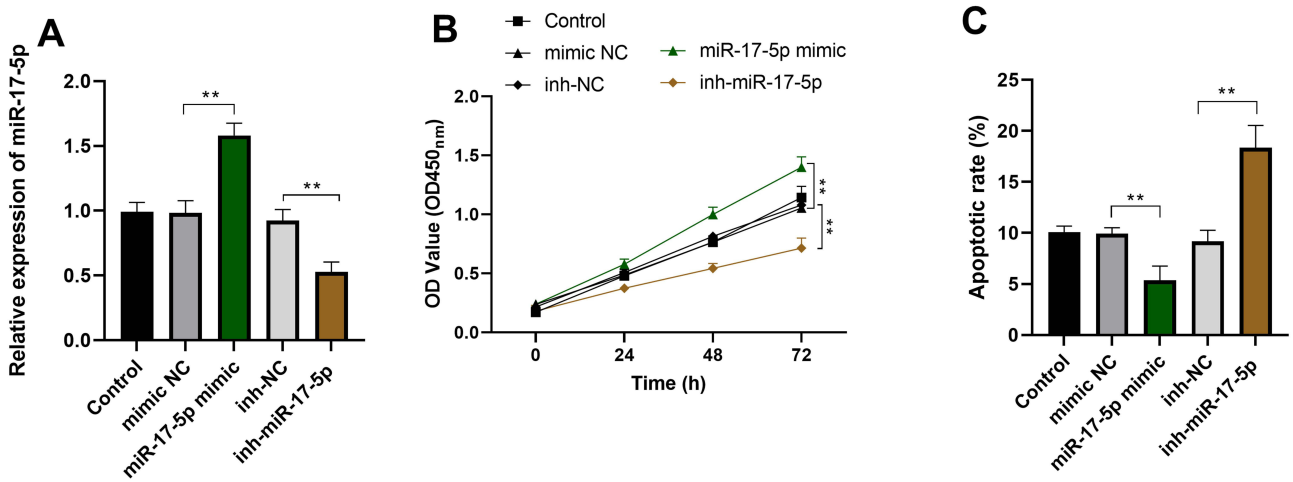

Figure 3 Effect of miR-17-5p on EPCs. Cell transfection efficiency (**A**). The CCK-8 assay was used to determine cell proliferation (**B**). Annexin V/PI flow cytometry for detection of cell apoptosis (**C**). ** P<0.01.

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Verification of the Targeting Relationship Between miR-17-5p and *FBXO48*

We screened for potential target genes of miR-17-5p and identified *FBXO48* as a candidate. Binding sites for both miR-17-5p and FBXO48 are illustrated in Figure 4A. Dual-luciferase reporter gene assay results corroborated the targeting relationship between miR-17-5p and *FBXO48* (Figure 4B). In EPCs, overexpression of miR-17-5p significantly inhibited *FBXO48* levels (Figure 4C). Moreover, *FBXO48* expression was notably elevated in T2DM patients compared to the control group (Figure 4D). Pearson correlation analysis revealed a significant negative correlation between serum miR-17-5p levels and *FBXO48* levels in T2DM patients ($r = -0.812$, $P < 0.001$) (Figure 4E).

Effect of miR-17-5p Targeting *FBXO48* on EPCs

RT-qPCR was used to detect the expressions of miR-17-5p and *FBXO48* after the cell transfection or co-transfection experiments. As shown in Figure 4F and G, in the miR-17-5p mimic group, the expression of miR-17-5p increased, and the expression level of *FBXO48* decreased. In the miR-17-5p mimic + oe *FBXO48* group, there was no significant difference in the expression of miR-17-5p, while the expression level of *FBXO48* increased. The results of the CCK-8 and apoptosis assays (Figure 4H and I) indicated that overexpression of miR-17-5p significantly promoted EPC proliferation and inhibited EPC apoptosis, while *FBXO48* counteracted this positive effect.

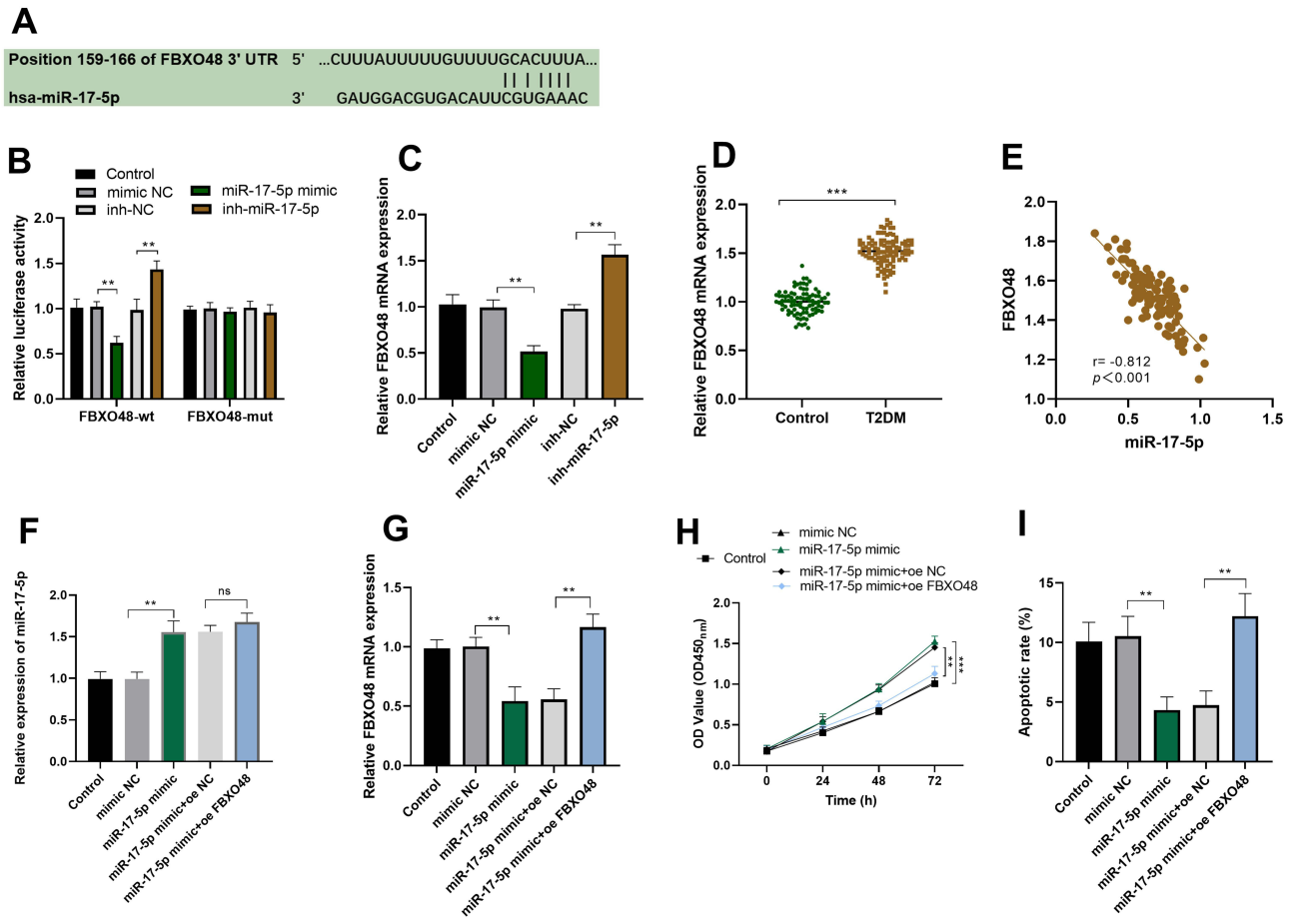

Figure 4 Regulation of miR-17-5p on EPCs Function by Targeting *FBXO48*. The binding site of miR-17-5p and *FBXO48* (**A**). The results of dual-luciferase reporter gene assay verified the targeting relationship between miR-17-5p and *FBXO48* (**B**). RT-qPCR was used to detect the expression level of *FBXO48* in EPCs. (**C**). The expression level of *FBXO48* in patients with T2DM was significantly higher than that in the control group (**D**). Correlation Analysis of Serum miR-17-5p and *FBXO48* Expression Levels in Patients with T2DM (**E**). Verification of Expression Levels of miR-17-5p and *FBXO48* in Co-transfection Experiments (**F** and **G**). Detection of EPCs Proliferation Ability in the Co-transfection Group by CCK-8 Assay (**H**). Detection of EPCs Apoptosis Rate in the Co-transfection Group by Flow Cytometry (**I**). ns P>0.05, ** P<0.01, *** P<0.001.

Discussion

MiRNAs have emerged as promising biomarkers for T2DM.[16] Research exploring the role of miRNAs in T2DM and its associated complications has underscored their potential utility in early diagnosis, treatment, and prognostication.[17] Serum miR-23a levels were found to be lower in patients with T2DM, making it a potential biomarker to diagnose prediabetes and T2DM.[18] Our study also revealed a significant decrease in the serum miR-17-5p levels in patients with T2DM, which was closely related to the patients' blood glucose indices. In addition, miR-17-5p showed high sensitivity and specificity in the diagnosis of T2DM. This suggests that miR-17-5p has the potential to serve as a biomarker for the early diagnosis of T2DM, which can help in the timely detection and intervention at the early stage of the disease, thus delaying the progression of the disease.

Patients with T2DM who failed to maintain optimal long-term blood glucose control were at risk of developing microvascular complications, which were the primary causes of morbidity and mortality in this cohort.[19] Nursing interventions tailored for T2DM patients can effectively manage blood sugar levels, mitigate the onset of complications, enhance overall quality of life, and contribute positively to the stabilization of their condition.[20] In our study, which involved a cohort of 100 patients with T2DM, we observed that 30 individuals developed chronic complications over a 5-year period, resulting in an incidence rate of 30%. Furthermore, early diagnosis and vigilant monitoring of T2DM are paramount in delaying or even preventing adverse outcomes.[21] MiRNAs have been shown to play an important role in the complications of T2DM in a large number of studies.[22] Existing studies have shown that low expression of miR-146a-5p is significantly associated with the occurrence of chronic complications in patients with type 1 diabetes mellitus, and its mechanism of action may be related to the regulation of inflammatory pathways.[23] In the field of T2DM complication prediction, this study found that low expression of miR-17-5p is closely related to T2DM chronic complications and has a good ability to identify and distinguish T2DM individuals without complications. Further mechanistic studies have confirmed that miR-17-5p can affect the function of EPCs by targeting and binding to the *FBXO48* gene, thereby participating in the pathological process of vascular complications. The differences in the mechanisms of action between the two miRNAs provide a subdivided direction for the precise development of intervention targets for T2DM complications and also lay a theoretical foundation for the design of subsequent targeted treatment strategies.

EPCs are a type of precursor cells that can proliferate and differentiate into mature endothelial cells, playing an important role in the occurrence and development of diabetes and its complications.[24] Dysfunction of EPCs is a core link in vascular complications of T2DM.[25] The vascular damage in diabetic patients is difficult to be repaired in a timely manner, increasing the risk of developing microvascular and macrovascular complications.[26] The proliferation and differentiation abilities of EPCs are inhibited, which affects the repair of blood vessels. Moreover, the increase in cell apoptosis leads to a reduction in the number of cells available for blood vessel repair.[27] Studies have shown that the proliferation capacity and apoptotic status of EPCs are subject to precise regulation by miRNA networks. For example, miR-126 promotes EPCs angiogenesis by targeting *SPRED1*.[28] Similar to miR-126, miR-17-5p maintains EPCs function by inhibiting negative regulatory factors. In this study, overexpression of *FBXO48* could reverse the protective effect of miR-17-5p on EPCs, which further confirms that *FBXO48* is a key effector molecule through which miR-17-5p regulates EPCs function. As a member of the F-box protein family, *FBXO48* can inhibit the AMPK signaling pathway by ubiquitin-mediated degradation of pAMPKα, thereby exacerbating insulin resistance.[29] This study found that the expression of *FBXO48* was increased in T2DM patients and was negatively correlated with miR-17-5p, which is consistent with the pathological-promoting role of FBXO48 in metabolic disorders in this study. In addition, Dong et al found that high glucose stabilizes thioredoxin-interacting protein (TXNIP) by downregulating miR-17 and activates the ASK1-p38 pathway to induce cell apoptosis.[30] In this study, *FBXO48* may participate in EPCs injury through a similar stress pathway, which provides a supplementary perspective for the multi-target regulation of miR-17-5p.

There are a number of weaknesses in this study. The included sample size was small, and all samples were from a single center, which may limit the generalizability of the conclusions. Therefore, multi-center large-sample cohort studies are needed to further verify its diagnostic and prognostic value. The detection method of miR-17-5p has not yet been standardized, and differences in sample processing, detection platforms, and data analysis may affect the

comparability of results. In addition, the in vitro EPCs model can only simulate functional changes at the single-cell level and cannot fully reproduce the complex microenvironment in the human vascular system. The correlation between its results and the in vivo physiological and pathological states needs to be further verified through animal models.

Conclusion

In conclusion, this study identified a notable reduction in serum miR-17-5p levels in patients with T2DM. By integrating the clinical data of these patients, we explored its potential as a biomarker for both T2DM and its associated chronic complications. Furthermore, investigating the effects of miR-17-5p targeting *FBXO48* on EPCs provided valuable insights into the diagnostic potential and underlying pathogenesis of T2DM and its microvascular complications.

Disclosure

The authors report no conflicts of interest in this work.

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