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ASSOCIATION BETWEEN LNCRNA-MALAT1 IN SERUM AND TYPE 2 DIABETES AND IT'S RISK FACTORS: A COMMUNITY-BASED CASE-CONTROL STUDY

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ABSTRACT

Background Previous studies have shown that long non coding RNA plays an important role in the occurrence and development of diabetes, and experimental studies also shown that LncRNA-MALAT1 was related to type 2 diabetes, but in the population, the correlation between serum LncRNA-MALAT1 expression level and type 2 diabetes has not been clarified. **Objective** To explore the relationship between serum LncRNA-MALAT1 expression level and the prevalence of type 2 diabetes, and to provide new ideas for exploring risk factors and new biomarkers of type 2 diabetes in the future. **Methods** 320 patients with type 2 diabetes newly diagnosed were selected as the case group, and 320 healthy people without endocrine system diseases were selected as the control group according to the 1:1 matching principle. The clinical data of these people were collected, and their peripheral blood was collected to detect the diagnostic indicators of diabetes, clinical biochemical indicators, and the expression of LncRNA-MALAT1 in serum by real-time fluorescent quantitative PCR, To analyze the association between human serum LncRNA-MALAT1 and type 2 diabetes, and the relationship between LncRNA-MALAT1 and related risk factors. **Results** The expression level of serum LncRNA-MALAT1 in the case group (3.24 ± 0.53) was significantly higher than that in the control group (1.124 ± 0.213). In patients with type 2 diabetes, the expression level of serum LncRNA-MALAT1 was positively correlated with fasting blood glucoser (r=0.612) and glycosylated hemoglobin (r=0.523), BMI (r=0.604), TC (r=0.517) and LDL (r=0.678)(P<0.05), but not with other indicators (P>0.05). Multiple logistic regression analysis showed that smoking (OR=2.144), hypertension history (OR=1.981), TC (OR=1.358) and LncRNA-MALAT1 (OR=2.632) were risk factors for type 2 diabetes, while regular exercise (OR=0.562) was a protective factor for diabetes. **Conclusion** The serum LncRNA-MALAT1 is highly expressed in patients with type 2 diabetes, and has correlation with diabetes related diagnostic indicators and lipid indicators. LncRNA-MALAT1 may be a new biomarker of type 2 diabetes.

KEYWORDS: Type 2 diabetes, long non coding RNA-MALAT1, risk factors, case-control study.

1. INTRODUCTION

In recent years, the prevalence of diabetes in China has been increasing year by year. According to the epidemiological survey data, the prevalence of diabetes among residents aged 18 and above in China rose from 7.7% in 1980 to 25.2% in 2018. At present, there are more than 140 million diabetes patients in China.[1,2] Diabetes has become one of the major public health problems in china.[3,4] Therefore, scholars have conducted extensive and in-depth research on the mechanism of the occurrence and development of diabetes.[5] Long non coding RNA(LncRNA) has been a hot research topic in the field of chronic diseases in recent years, with a large number of studies reporting that it is related to the occurrence, development, and prognosis of many diseases. However, there are few reports on the function and significance of long-chain non coding RNA in type 2 diabetes.[6] LncRNA lung cancer metastasis associated transcript 1 (MALAT) is a widely studied LncRNA. MALAT1 is widely expressed in various tissues, and initial research mainly focused on its relationship with tumors.[7,8] However, studies have shown that LncRNA-MALAT1 was closely related to diabetes and diabetes complications.[9] A Chinese study found that the level of Lnc-MALAT1 in the serum of pregnant women with diabetes increased.[10] Liu et al.[11] used sh-MALAT1 to silence the expression of MALAT1 in human umbilical vein endothelial cells in their study, and found that after MALAT1 silencing, resistance, angiotensin II, and tumor necrosis factor (TNF) were inhibited-α, the expression levels of interleukin-6 (IL-6) and soluble intercellular adhesion molecule-1 (sICAM-1)

decreased, leading to reduced insulin resistance. Additionally, in a mouse model, exercise was observed to downregulate MALAT1 levels, reducing the occurrence of insulin resistance. Yan et al.[12] found that hyperglycemia could increase the expression of MALAT1 in retinal endothelial cells and the retina of diabetes rats. Silencing the expression of MALAT1 can significantly alleviate retinal vascularization, vascular leakage and retinal inflammation induced by diabetes. In cardiomyocytes of diabetes rats, the down-regulation of Lnc-MALAT1 can protect cardiomyocytes and improve cardiac function.[13] In other studies, MALAT1 is highly expressed in the renal cortex of diabetes nephropathy mice, which can β-Catenin translocates to the nucleus and enhances the expression of serine/arginine splicing factor 1, leading to damage to renal podocytes. Early silencing of MALAT1 resulted in partial recovery of podocyte function.[14]

Although the above research showed that LncRNA-MALAT1 was closely related to the occurrence and development of diabetes and its complications, the research on the association between LncRNA MALAT1 and type 2 diabetes was still limited. This study aims to explore the relationship between the expression of LncRNA-MALAT1 in human serum and type 2 diabetes and its risk factors, so as to provide new ideas for exploring the role of LncRNA in type 2 diabetes in the future.

2. RESEARCH METHODS

2.1 Objects selection: 320 newly diagnosed type 2 diabetes patients in the community from March 2023 to July 2023 were selected as the case group. According to the principle of gender equality, age difference not exceeding 2 years, similar hometown and economic situation, healthy individuals who underwent physical examination at the same hospital were selected as the control group in a 1:1 ratio. All blood samples and information collection of the study subjects were obtained with the informed consent of the patients.

2.2 Case inclusion criteria: ① Age ≥18 years old. Refer to the diagnostic criteria for type 2 diabetes in the Guidelines for the Prevention and Treatment of Type 2 diabetes in China (2020). The patient was newly diagnosed with diabetes, who has no history of secondary diabetes and has not taken hypoglycemic drugs in the past. Other major diseases such as tumor, infection and infectious diseases are excluded, and he can complete the questionnaire survey and related items of this physical examination.

2.3 Selection criteria for the control group: subjects ≥ 18 years old, who have no previous history of diabetes, and whose fasting blood glucose was normal during physical examination at the time of enrollment. Through medical history and physical examination, there was no secondary diabetes, malignant tumor, other endocrine system diseases, autoimmune diseases, psychiatric history or family history of psychosis, serious heart, liver, kidney diseases, recent infection and other major diseases.

2.4 Diagnostic criteria: BMI<18.5 indicated underweight,18.5 ≤BMI＜24 indicates normal body weight, 24≤BMI＜28 was considered overweight, BMI ≥28 indicates obesity. Smoking refer to the subject smoking more than 100 cigarettes so far and continuing to smoke. Drinking alcohol refer to drinking alcohol at least once a week. Adequate sleep: refer to an average total daily sleep time ≥8 hours in the past 2 weeks. Family history of diabetes refer to that any of the subjects' immediate family members has diabetes.

Data collection methods: (1) A questionnaire was used to collect records of the study subjects, including age, gender, occupation, smoking, alcohol consumption, family history of hypertension, medical history, and medication history. (2) The height, weight, blood pressure, heart rate, fasting blood glucose, glycated hemoglobin (HbA1c), blood lipids, insulin, cortisol, and other indicators of all participants were detected. The oral glucose tolerance test (OGTT) began at 8 o'clock the next day on an empty stomach. 75g of anhydrous glucose was dissolved in 200-300ml of warm water and consumed within 5 minutes. Blood collection was immediately initiated and specimens were sent for testing. Use the insulin resistance index (HOMA-IR) to evaluate the patient's insulin resistance, calculated as HOMA-IR=FPG × Fasting insulin/22.5.

2.6 Reagents and instruments: TRIzol (Gibeo company) and RT-PCR reagents (Takara company); Reverse transcription reagent kit Fermentas K1622, TurboAct Transfer Agents (Thermo Scientific), qPCR reagent kit (Promega company); PCR primers, PCR internal reference primers (Shanghai Shenggong Company).

2.7 Total RNA extraction and identification of purity and content: The serum obtained from isolation was melted on ice, Take 250 μl serum sample, add 750μl Trizol, extract total RNA according to the instructions of the Trizol reagent. Measure the total RNA concentration and purity using a spectrophotometer.

2.8 qPCR detection of LncRNA-MALAT1 expression: Total RNA of each cell was reverse transcribed into cDNA using Fermentas K1622 reagent. The main steps are as follows: Total RNA 1 μg. Random Hexamer Primer (0.2 μg/ul) 1 μl. Nuclease free Water To 12 μl. 65 ℃ for 5 minutes, immediately place on ice for 2-3 minutes. After cooling the sample on ice, add the following reaction system: 5 × Reaction Buffer 4 μl. RiboLockTMRNase Inhibitor 1 μl. Transcriptase (200U/ μl) 1 μl. 10mM dNTP Mix 2 μl. Incubate at 25 ℃ for 5 minutes, then incubate at 42 ℃ for 60 minutes, and treat at 70 ℃ for 5 minutes to inactivate reverse transcriptase. After reverse transcription into cDNA, configure the

QPCR system according to the reagent instructions (20 μl) : 2 × Master Mix (10 μl) Primer sequence: MALAT1: Upstream 5'-CAGACCACCAGGTTTACAG3', Downstream 5'-GACCATCCAATGCTTCA-3',GADPH: Upstream 5'- GACTTCAACAGCGACACCA-3', Downstream 5'- CACCCTGTTGCTAGCCAAA-3'. Each sample has 3 replicates per gene. Set the QPCR reaction program on the ABI Stepone Plus qPCR instrument at 95 ℃ for 15 minutes; 95 ℃, 10s; 60 ℃, 20 seconds, 40 cycles; 72 ℃, 15s, 95 ℃, 15s; 60 ℃ for 1 minute; 95 ℃ for 15 seconds. With $2^{-\Delta\Delta Ct}$ value represented the expression level of LncRNA MALAT1.

2.9 Statistical methods SPSS 20.0 statistical software was used to establish a database and conduct statistical analysis. All the data are represented as rate (%) , median, mean ± standard deviation (SD; $\bar{x} \pm s$) of three or more independent experiments. Comparisons were done using the chi square test for rate (%) from several independent experiments and Student's t-test. Multivariate analysis uses multiple logistic regression, and linear correlation analysis was used to analyze the correlation between variables. A value of P<0.05 was considered statistically significant.

2.10 Ethical statement: All the human experiements were performed in accordance with the principals of the Declaration of Helsinki. All experimental protocols were approved by Research ethics committee of Pingshan hospital of Southern Medical University. The personal information of samples involved in the study was not opened and all patients have informed consent.

3.RESULTS

3.1 Comparison of demographic data between two groups The case group and control group included in this study were composed of 320 individuals, with a total of 168 males and 152 females. Among them, the average age of the case group was 46.51 ± 8.17 years (31-73 years), while the average age of the control group was 46.21 ± 8.22 years (31-72 years), with no statistical difference (P>0.05), indicating comparability.

3.2 Comparison of life behavior and hypertension history between two groups The smoking rate (26.87%) and hypertension history (27.19%) in the case group were significantly higher than those in the control group (20.00% and 15.63%), while the regular exercise rate (27.19%) and sleep adequacy rate (65.93%) were significantly lower than those in the control group (31.56% and 73.13%), with statistical significance (P<0.01). There was no statistically significant difference in alcohol consumption and BMI between the case group and the control group (P>0.05)(Table 1).

Table 1 Comparison of life behavior and hypertension history between case group and control group population.

Items	Case group (n=320)	Control group (n=320)	P value
Smokingn,%)	86(26.87)	64(20.00)	<0.01
Drinking(n,%)	76(23.75)	73(22.81)	>0.05
Regular exercise(n,%)	87(27.19)	101(31.56)	<0.05
Sleep adequacy(n,%)	211(65.93)	234(73.13)	<0.01
BMI(kg/m^2)	24.81±6.88	25.77±6.58	>0.05
Hypertension history(n,%)	87(27.19)	50(15.63)	<0.01

3.3 Comparison of clinical biochemical results between two groups The fasting blood glucose (7.86 ± 0.98 mmol/L), HbA1c(10.21 ± 2.17%), TC5.78 ± 0.52 mmol/L, and LDL (2.99 ± 0.38 mmol/L) of the case group were all higher than those of the control group, while the fasting insulin (51.68 ± 15.62 pmol/L) of the case group was significantly lower than that of the control group (63.33 ± 18.62 pmol/L), with statistical significance (P<0.05). There was no statistically significant difference (P>0.05) in the results of other clinical biochemical indicators between the two groups of people. Shown in Table 2.

Table 2: Comparison of clinical biochemical index results between case group and control group population.

Items	Case group (n=320)	Control group (n=320)	P value
Fasting blood glucose(mmol/L)	7.86±0.98	5.04±0.72	<0.001
HbA1c(%)	10.21±2.17	5.61±0.81	<0.001
Fasting insulin(pmol/L)	51.68±15.62	63.33±18.62	<0.001
HOMA-IR	2.28±1.41	2.044±0.94	>0.05
Cortisol(mmol/L)	392.54±48.52	381.96±49.88	>0.05
TC(mmol/L)	5.78±0.52	4.81±0.49	<0.01
TG(mmol/L)	1.54±0.34	1.32±0.25	>0.05
HDL(mmol/L)	1.12±0.18	1.21±0.31	>0.05
LDL(mmol/L)	2.99±0.38	2.12±0.25	<0.05
Blood creatinine(μmol/L)	75.69±15.63	70.22±18.23	>0.05

3.4 Relationship between serum LncRNA-MALAT1 expression level and diabetes related indicators in the two groups The expression level of serum LncRNA-MALAT1 in the two groups was detected by qPCR technology. The results showed that the expression level of serum LncRNA-MALAT1 in the case group was (3.24 ± 0.53) significantly higher than that in the control group (1.124 ± 0.213). Glycated hemoglobin showed a positive correlation ($r_{\text{fasting blood glucose}}$=0.612, P<0.001; $r_{\text{glycated hemoglobin}}$=0.523, P<0.001), with statistical significance (P<0.01).

3.5 The correlation between LncRNA-MALAT1 and clinical biochemical indicators The correlation analysis was used to explore the correlation between LncRNA-MALAT1 and clinical biochemical indicators. The results showed that LncRNA-MALAT1 in serum was positively correlated with BMI, TC, and LDL, but not with other indicators (P>0.05), as shown in Table 3.

Table 3: Correlation analysis between LncRNA-MALAT1 and clinical biochemical indicators in serum.

Items	r值	P值
BMI(kg/m^2)	0.604	<0.01
TC(mmol/L)	0.5171	<0.01
TG(mmol/L)	0.487	>0.05
HDL(mmol/L)	0.397	>0.05
LDL(mmol/L)	0.678	<0.01
Cortisol(mmol/L)	0.688	>0.05
Blood creatinine(μmol/L)	0.511	>0.05

3.6 Multivariate logistic regression analysis of influencing factors of diabetes On the basis of univariate logistic regression analysis, significant factors with univariate analysis were introduced for multivariate logistic regression analysis. The Backward: LR method was used to establish a regression model and screen out four influencing factors, including smoking (OR=2.144), regular exercise (OR=0.562), and history of hypertension (OR=1.981) , TC (OR=1.358) and LncRNA-MALAT1 (OR=2.632), the results suggested that smoking, hypertension history, TC and LncRNA-MALAT1 history were risk factors for diabetes, and regular exercise was a protective factor for diabetes, as shown in Table 4.

Table 4: Multi factor conditional logistic regression analysis results of influencing factors of diabetes.

	B	S.E.	Wald	df	P	OR(95%CI)
smoking	0.782	0.231	2.482	1	0.000	2.144(1.214-3.551)
regular exercise	-0.601	0.202	-0.512	1	0.021	0.562(0.145-0.854)
Sleep adequacy	-0.125	0.152	-0.454	1	0.003	0.741(0.118-1.116)
hypertension history	0.464	0.184	15.898	1	0.001	1.981(1.121-3.004)
TC	0.251	0.084	3.241	1	0.000	1.358 (1.135-1.891)
LncRNAMALAT	0.851	0.214	10.521	1	0.001	2.632(1.833-4.522)

4. DISCUSSION

At present, diabetes has become one of the most common chronic diseases in China. Medical institutions and scholars all over China have paid special attention to diabetes, and the prevention and treatment of diabetes has become one of the indicators assessed by governments all over China.

In recent years, scholars around the world have made extensive exploration on the research of biomarkers related to the pathogenesis, development and prognosis of diabetes. Among them, the research on the association between long chain non coding RNA and diabetes has received more and more attention from the academic community. LncRNA is a type of RNA molecule with a transcript length exceeding 200 nt. Recent studies have shown that LncRNA can regulate various biological processes and is related to the occurrence and development of diseases. It can serve as a biomarker for disease diagnosis, treatment, and prognosis.[15] LncRNA is believed to be associated with cell differentiation, proliferation, metabolism, and various life activities, and is involved in the occurrence and development of many diseases.[16-19] At present, studies have pointed out that many kinds of LncRNAs are closely related to the occurrence and development of diabetes and its complications, including H19[20], MEG3[21], uc.322[22], etc. Previous studies have shown that the blood sugar of diabetes patients is related to LncRNA-MALAT1, and that the increased expression of LncRNA-MALAT1 will lead to poor blood sugar control in diabetes patients and accelerate the occurrence of complications. Recent studies also show that LncRNA-MALAT1 is involved in the pathogenesis of diabetes nephropathy[23] and diabetes retinopathy.[24]

This study explored the relationship between LncRNA-MALAT1 and type 2 diabetes and its risk factors through case control study. The results showed that the expression level of serum LncRNA-MALAT1 in the case group was significantly higher than that in the control

group. In diabetes patients, the expression level of serum LncRNA-MALAT1 is correlated with diabetes related indicators and clinical detection indicators such as BMI, TC and LDL. Multiple logistic regression analysis showed that the overexpression of LncRNA-MALAT1 was a risk factor for type 2 diabetes. The results suggest that human serum LncRNA-MALAT1 is associated with type 2 diabetes, and the high expression of this factor is related to the risk factors of type 2 diabetes. Studies have shown that lncLSTR, lncRNA-DYNLRB2-2, lncRNA Lexis, lncRNAHULC, and lnc-HC were associated with lipid metabolism.[25,26] This study also showed a correlation between serum LncRNA-MALAT1 and TC and LDL. These results suggest that LncRNA-MALAT1 may be a potential new biomarker for type 2 diabetes.

The results of this study are consistent with current literature, indicating that LncRNA-MALAT1 may affect the body's feedback regulation of hyperglycemia. Research has shown that the correct response of the body to high blood sugar is to secrete more insulin to reduce excessive blood sugar. LncRNA-MALAT1 may affect the elevation of blood sugar by inhibiting the active secretion of insulin on high blood sugar. Research also showed that LncRNA-MALAT1 could inhibit the proliferation of breast cancer by downregulating the expression of miR124 and inhibiting the CDK4/E2F1 signaling pathway, which is an important pathway affecting insulin secretion. But further research is needed to prove the connection between them.

This study found that LncRNA-MALAT1 is associated with type 2 diabetes, but how is it related to the development and prognosis of type 2 diabetes? Further research is needed. In the past, our research team has found that LncRNA-MALAT1 can regulate DNA damage and repair channels in human bronchial epithelial cells, and affect cell proliferation and apoptosis.[27] However, whether the regulatory function and mechanism of LncRNA-MALAT1 on type 2 diabetes also have the above findings remains to be verified later.[28] In the future, we will continue to increase the sample size of the enrolled patients, and carry out regular follow-up and examination to provide scientific basis for comprehensively exploring the role of LncRNA-MALAT1 in the occurrence, development and prognosis of type 2 diabetes.

CONFLICT OF INTEREST The authors have declared that no competing interests exist.

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