Association of Long Non-coding RNA NEAT1 and miRNA-182-5p with Liver Fibrosis Risk in Type 2 Diabetes Mellitus: A Postprint

Authors: He Jia, Li Yongping, Wei Feng, Liu Meilan, Wu Yaling, Shao Longge, Wei Feng

Date: 2023-07-24T00:00:00+00:00

Abstract

Background As the incidence of chronic metabolic diseases continues to rise annually, posing a threat to public health, research on non-coding RNAs and endocrine metabolism-related diseases has become a hotspot both domestically and internationally. However, few reports exist on long non-coding RNA nuclear-enriched abundant transcript 1 (lncRNA NEAT1) and microRNA (miRNA)-182-5p in type 2 diabetes mellitus (T2DM) complicated with metabolism-associated fatty liver disease (MAFLD).

Objective To investigate the mechanism and clinical significance of lncRNA NEAT1 and miRNA-182-5p in the occurrence and development of liver fibrosis in patients with T2DM complicated with MAFLD.

Methods A total of 236 T2DM patients who visited the Department of Endocrinology at The First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology between October 2021 and June 2022 were enrolled as study subjects, while 49 healthy individuals were included as a healthy control group. General data and laboratory test results were collected. Visceral fat area (VFA) and subcutaneous fat area (SFA) were measured. Peripheral blood was collected to determine lncRNA NEAT1 and miRNA-182-5p. The T2DM patients were divided into a T2DM without MAFLD group (n=82) and a T2DM with MAFLD group (n=154). Furthermore, based on the fibrosis index (FIB-4), the T2DM with MAFLD group was subdivided into a low-risk fibrosis subgroup (n=55), an intermediate-risk fibrosis subgroup (n=69), and a high-risk fibrosis subgroup (n=30). Additionally, healthy individuals undergoing physical examination were selected as the control group (n=49). Spearman rank correlation analysis was used to explore the correlation between lncRNA NEAT1 and miRNA-182-5p expression levels in the high-risk fibrosis

subgroup, and multivariate ordinal Logistic regression analysis was employed to investigate the influencing factors of liver fibrosis risk.

Results The healthy control group had lower age, neck circumference (NC), fasting plasma glucose (FPG), and glycated hemoglobin (HbA1c), and higher albumin (Alb) than both the T2DM with MAFLD group and the T2DM without MAFLD group, with statistically significant differences (P<0.05). The T2DM with MAFLD group had higher body mass index (BMI), waist circumference (WC), VFA, SFA, homeostasis model assessment of insulin resistance (HOMA-IR), triglycerides (TG), serum uric acid (SUA), and lncRNA NEAT1, lower platelet count (PLT) than both the healthy control group and the T2DM without MAFLD group, and lower total cholesterol (TC) than the healthy control group, with statistically significant differences (P<0.05). The T2DM without MAFLD group had higher HOMA-IR and lncRNA NEAT1 than the healthy control group, higher miRNA-182-5p than both the healthy control group and the T2DM with MAFLD group, and lower alanine aminotransferase (ALT) and aspartate aminotransferase (AST) than both the healthy control group and the T2DM with MAFLD group, with statistically significant differences (P<0.05). The low-risk fibrosis subgroup had lower VFA, SFA, AST, and lncRNA NEAT1, higher PLT and miRNA-182-5p than both the intermediate-risk and high-risk fibrosis subgroups, lower BMI, WC, and NC than the high-risk fibrosis subgroup, and higher TC than the high-risk fibrosis subgroup, with statistically significant differences (P<0.05). The intermediate-risk fibrosis subgroup had higher PLT and miRNA-182-5p, and lower AST and lncRNA NEAT1 than the high-risk fibrosis subgroup, with statistically significant differences (P<0.05). Spearman rank correlation analysis revealed that lncRNA NEAT1 was significantly negatively correlated with miRNA-182-5p in patients in the high-risk fibrosis subgroup (rs=-0.438, P<0.05). Multivariate ordinal Logistic regression analysis showed that lncRNA NEAT1 [OR=1.326, 95%CI (1.087, 1.616)], VFA [OR=1.019, 95%CI (1.006, 1.033)], miRNA-182-5p [OR=0.083, 95%CI (0.027, 0.257)], PLT [OR=0.956, 95%CI (0.942, 0.970)], and AST [OR=1.048, 95%CI (1.022, 1.075)] were influencing factors for liver fibrosis risk in T2DM patients with MAFLD.

Conclusion Peripheral blood lncRNA NEAT1 and miRNA-182-5p are closely associated with liver fibrosis in patients with T2DM complicated with MAFLD, providing new evidence for the early prediction, diagnosis, and treatment of this disease.

Full Text

Correlation of Long Non-coding RNA NEAT1 and miRNA-182-5p with Liver Fibrosis Risk in Patients with Type 2 Diabetes Mellitus

JIA He[1], YONG-PING Li[2], FENG Wei[1]*, MEI-LAN Liu[1], YA-LING Wu[1], LONG-GE Shao[1]

[1]The First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou 014010, China
[2]Comprehensive Support Center, Baotou Health Commission, Baotou 014010, China
*Corresponding author: WEI Feng, Chief Physician/Professor; E-mail: 1135172562@qq.com
HE Jia and LI Yongping are co-first authors

Abstract

Background: With the rising incidence of chronic metabolic diseases posing a threat to public health, research on non-coding RNAs in endocrine and metabolic disorders has become a global hotspot. However, studies on long non-coding RNA nuclear enriched abundant transcript 1 (lncRNA NEAT1) and microRNA (miRNA)-182-5p in type 2 diabetes mellitus (T2DM) complicated with metabolic-associated fatty liver disease (MAFLD) remain scarce.

Objective: To investigate the mechanism and clinical significance of lncRNA NEAT1 and miRNA-182-5p in the development of liver fibrosis in T2DM patients with MAFLD.

Methods: A total of 236 T2DM patients admitted to the Endocrinology Department of the First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology between October 2021 and June 2022 were enrolled as study subjects, along with 49 healthy individuals as healthy controls. General information and laboratory test results were collected. Visceral fat area (VFA) and subcutaneous fat area (SFA) were measured. Peripheral blood samples were collected to determine lncRNA NEAT1 and miRNA-182-5p expression levels. T2DM patients were divided into a T2DM without MAFLD group (n=82) and a T2DM with MAFLD group (n=154). The T2DM with MAFLD group was further stratified into low-risk (n=55), medium-risk (n=69), and high-risk (n=30) subgroups based on the fibrosis index (FIB-4). Spearman rank correlation analysis was used to explore the relationship between lncRNA NEAT1 and miRNA-182-5p expression in the high-risk subgroup, while multivariate ordinal logistic regression was employed to identify factors influencing liver fibrosis risk.

Results: The healthy control group showed significantly lower age, neck circumference (NC), fasting plasma glucose (FPG), and glycated hemoglobin (HbA1c) compared to both T2DM groups, while albumin (Alb) levels were significantly higher ($P<0.05$). The T2DM with MAFLD group exhibited significantly higher BMI, waist circumference (WC), VFA, SFA, homeostatic model assessment for insulin resistance (HOMA-IR), triglycerides (TG), serum uric acid (SUA), and lncRNA NEAT1, but lower platelet count (PLT) and total cholesterol (TC) compared to the healthy control and T2DM without MAFLD groups ($P<0.05$). The T2DM without MAFLD group showed higher HOMA-IR and lncRNA NEAT1 than healthy controls, while miRNA-182-5p was higher than in both other

groups, and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were lower (P<0.05). Across fibrosis risk subgroups, VFA, SFA, AST, and lncRNA NEAT1 progressively increased from low to high risk, while PLT and miRNA-182-5p decreased significantly (P<0.05). Spearman analysis revealed a significant negative correlation between lncRNA NEAT1 and miRNA-182-5p in the high-risk subgroup (rs=-0.438, P<0.05). Multivariate ordinal logistic regression identified lncRNA NEAT1 [OR=1.326, 95%CI (1.087, 1.616)], VFA [OR=1.019, 95%CI (1.006, 1.033)], miRNA-182-5p [OR=0.083, 95%CI (0.027, 0.257)], PLT [OR=0.956, 95%CI (0.942, 0.970)], and AST [OR=1.048, 95%CI (1.022, 1.075)] as independent factors influencing liver fibrosis risk in T2DM patients with MAFLD.

Conclusion: Peripheral blood lncRNA NEAT1 and miRNA-182-5p are closely associated with liver fibrosis development in T2DM patients with MAFLD, providing novel biomarkers for early prediction, diagnosis, and treatment of this condition.

Keywords: Type 2 diabetes mellitus; Metabolic-associated fatty liver disease; NEAT1; miRNA-182-5p; Hepatic fibrosis; Risk factor analysis

Introduction

Type 2 diabetes mellitus (T2DM) is a common chronic metabolic disease with complex pathogenesis primarily involving insulin resistance (IR) and pancreatic β-cell dysfunction [1], both of which influence disease progression throughout its course. Epidemiological surveys project that the global prevalence of diabetes will reach 784 million (12.2%) by 2045 [2]. T2DM is frequently complicated by metabolic-associated fatty liver disease (MAFLD), which was renamed from non-alcoholic fatty liver disease (NAFLD) following a 2020 international expert consensus statement that MAFLD better describes liver diseases associated with endocrine and metabolic dysfunction [3]. Approximately 55.5% of T2DM patients have coexisting MAFLD, with 17.0% developing fibrosis [4]. This combination increases the risk of cirrhosis, hepatocellular carcinoma, diabetic nephropathy, and cardiovascular complications, posing a serious threat to human health.

The pathogenesis of T2DM with MAFLD is intricate. Non-coding RNAs have emerged as a research hotspot in this field. Long non-coding RNA nuclear enriched abundant transcript 1 (lncRNA NEAT1) is closely associated with embryonic development, cell proliferation and differentiation, steatosis, oxidative stress, and endoplasmic reticulum stress [5]. Studies have shown that lncRNA NEAT1 participates in regulating insulin synthesis, secretion, and sensitivity [6]. MicroRNAs (miRNAs) represent another class of non-coding RNAs, among which miRNA-182-5p has been demonstrated to play a role in T2DM and its complications by regulating various signaling pathways that modulate IR [7]. However, research on lncRNA NEAT1 and miRNA-182-5p in T2DM with

MAFLD remains limited. This study investigated the expression of these non-coding RNAs in peripheral blood of different patient groups and analyzed their correlation with liver fibrosis to provide new insights for early clinical diagnosis and disease prevention.

Methods

Study Subjects

We enrolled 236 T2DM patients who visited the Endocrinology Department of the First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology between October 2021 and June 2022 and were admitted to the National Metabolic Management Center (MMC). Additionally, 49 healthy individuals undergoing physical examination at the same hospital were included as healthy controls. The study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Baotou Medical College (approval number: 2023011), and all participants provided informed consent.

Inclusion criteria were: (1) T2DM diagnosis according to the "Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus (2020 Edition)" [8,9]; (2) MAFLD diagnosis based on the "International Expert Consensus Statement on the New Definition of Metabolic Dysfunction-Associated Fatty Liver Disease" [3]; and (3) age between 18-80 years. Exclusion criteria included: (1) other types of diabetes or acute diabetic complications; (2) infectious, immune, or malignant diseases; (3) severe hepatic or renal insufficiency; and (4) recent use of medications affecting liver function.

General data collected included age, sex, T2DM duration, smoking history (defined as $ $1 cigarette/day for >1 year [10]), and alcohol consumption (defined as $ $100 mL/day of spirits [alcohol content >50%] for >1 year [10]). Anthropometric measurements included height, weight, neck circumference (NC), and waist circumference (WC), from which BMI was calculated.

Laboratory Measurements

All participants underwent measurement of platelet count (PLT), fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (Alb), triglycerides (TG), total cholesterol (TC), serum uric acid (SUA), and fasting C-peptide. The modified homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as: HOMA-IR = 1.5 + FPG (mmol/L) × fasting C-peptide (pmol/L) / 2800.

Measurement of Visceral and Subcutaneous Fat Areas

VFA and SFA were measured using bioelectrical impedance analysis (Omron DUALSCAN HDS-2000) and expressed in cm^2.

Detection of lncRNA NEAT1 and miRNA-182-5p

Peripheral blood (2 mL) was collected from each subject. Mononuclear cells were isolated using human lymphocyte separation medium, and total RNA was extracted using the Trizol method. Relative expression levels of lncRNA NEAT1 and miRNA-182-5p were detected by quantitative real-time PCR (qRT-PCR). For lncRNA NEAT1, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) served as the internal reference, with detection performed according to kit instructions (Tiangen Biotech, catalog: FP402-02). For miRNA-182-5p, U6 served as the internal reference, following kit instructions (Vazyme, catalog: MQ101-02). Primers were synthesized by Sangon Biotech (Shanghai) Co., Ltd., with sequences shown in Table 1 .

Grouping

T2DM patients were divided into T2DM without MAFLD (n=82) and T2DM with MAFLD (n=154) groups based on the international expert consensus statement [3]. The T2DM with MAFLD group was further stratified using the fibrosis index (FIB-4): FIB-4 = (age × AST) / (PLT × $ALT^{1}/^{2}$) [11]. Low-risk subgroup: FIB-4 $<$ 1.30 or age $\geq$ 65 years with FIB-4 $<$ 2.0 (n=55); medium-risk subgroup: 1.30 $\leq$ FIB-4 $\leq$ 2.67 or age $\geq$ 65 years with 2.00 $\leq$ FIB-4 $\leq$ 2.67 (n=69); high-risk subgroup: FIB-4 $>$ 2.67 (n=30). Healthy controls (n=49) were included for comparison.

Statistical Analysis

Data were analyzed using SPSS 26.0 software. The Kolmogorov-Smirnov test assessed normality. Normally distributed continuous variables were expressed as mean $\pm$ standard deviation, with one-way ANOVA for multi-group comparisons and LSD-t test for pairwise comparisons. Non-normally distributed variables were presented as median (P25, P75), with Kruskal-Wallis H test for multi-group comparisons and Mann-Whitney U test for pairwise comparisons. Categorical data were expressed as percentages and compared using ^{2} test. Spearman rank correlation analysis examined the relationship between lncRNA NEAT1 and miRNA-182-5p in the high-risk subgroup. Multivariate ordinal logistic regression analysis identified factors influencing liver fibrosis risk. Statistical significance was defined as P $<$ 0.05.

Results

Comparison Among T2DM Without MAFLD, T2DM With MAFLD, and Healthy Control Groups

Significant differences were observed among the three groups in age, BMI, NC, WC, VFA, SFA, FPG, HbA1c, HOMA-IR, PLT, ALT, AST, Alb, TG, TC, SUA, lncRNA NEAT1, and miRNA-182-5p (P<0.05). The healthy control group had significantly lower age, NC, FPG, and HbA1c, and higher Alb compared to

both T2DM groups (P<0.05). The T2DM with MAFLD group showed significantly higher BMI, WC, VFA, SFA, HOMA-IR, TG, SUA, and lncRNA NEAT1, but lower PLT and TC compared to healthy controls and T2DM without MAFLD (P<0.05). The T2DM without MAFLD group had higher HOMA-IR and lncRNA NEAT1 than healthy controls, higher miRNA-182-5p than both other groups, and lower ALT and AST than both other groups (P<0.05). No significant differences were found in sex distribution, T2DM duration, smoking history, or alcohol consumption among the three groups. Detailed data are presented in Table 2 .

Comparison Among Liver Fibrosis Risk Subgroups

Significant differences were observed among low-, medium-, and high-risk subgroups in sex distribution, BMI, NC, WC, VFA, SFA, PLT, AST, TC, lncRNA NEAT1, and miRNA-182-5p (P<0.05). The low-risk subgroup had significantly lower VFA, SFA, AST, and lncRNA NEAT1, but higher PLT and miRNA-182-5p compared to medium- and high-risk subgroups. BMI, WC, and NC were lower in the low-risk subgroup compared to the high-risk subgroup, while TC was higher (P<0.05). The medium-risk subgroup showed higher PLT and miRNA-182-5p but lower AST and lncRNA NEAT1 compared to the high-risk subgroup (P<0.05). No significant differences were found in age, T2DM duration, smoking history, alcohol consumption, FPG, HbA1c, HOMA-IR, ALT, Alb, TG, or SUA among the three subgroups. Detailed data are presented in Table 3 .

Correlation Between lncRNA NEAT1 and miRNA-182-5p in High-Risk Subgroup

Spearman rank correlation analysis revealed a significant negative correlation between lncRNA NEAT1 and miRNA-182-5p in the high-risk subgroup (rs = -0.438, P < 0.05).

Multivariate Analysis of Liver Fibrosis Risk Factors

Multivariate ordinal logistic regression analysis was performed with liver fibrosis risk level as the dependent variable (1=low-risk, 2=medium-risk, 3=high-risk) and sex, lncRNA NEAT1, miR-182-5p, BMI, NC, WC, VFA, SFA, AST, PLT, and TC as independent variables. The results identified lncRNA NEAT1 [OR=1.326, 95%CI (1.087, 1.616)], VFA [OR=1.019, 95%CI (1.006, 1.033)], miRNA-182-5p [OR=0.083, 95%CI (0.027, 0.257)], PLT [OR=0.956, 95%CI (0.942, 0.970)], and AST [OR=1.048, 95%CI (1.022, 1.075)] as independent influencing factors for liver fibrosis risk in T2DM patients with MAFLD (P<0.05). Detailed results are presented in Table 4 .

Discussion

Changes in dietary patterns have led to increasing incidence of obesity, diabetes, and fatty liver disease, becoming major global health concerns. MAFLD has replaced chronic hepatitis as the most common chronic liver disease worldwide [12]. The widely accepted pathogenic mechanism is the "multiple-hit" hypothesis, wherein unhealthy diet, lifestyle, environmental and genetic factors lead to IR, obesity, metabolic disorders, oxidative stress, and mitochondrial dysfunction, collectively causing hepatocyte injury and fibrosis that may progress to cirrhosis. Therefore, early monitoring and identification of fibrosis risk are crucial for patient prognosis. Although liver biopsy remains the gold standard for diagnosing fibrosis, its invasive nature and common complications have led to widespread adoption of the FIB-4 index for assessing fibrosis severity [11].

Our study found that T2DM patients with MAFLD had significantly elevated BMI, WC, VFA, SFA, and TG, indicating more severe fat accumulation and metabolic abnormalities. This suggests that increased body weight and abdominal obesity may augment MAFLD risk in T2DM patients. Compared with low-risk patients, those in the high-risk fibrosis subgroup showed significantly increased AST, VFA, SFA, BMI, NC, and WC. Multivariate analysis confirmed VFA as an independent risk factor for fibrosis, with higher VFA levels associated with greater fibrosis risk. Yu et al. [12] demonstrated that increased VFA independently correlates with non-alcoholic steatohepatitis and fibrosis, suggesting VFA may be a central target for lifestyle interventions in MAFLD patients. The pathological mechanisms of visceral adipose tissue (VAT) may involve: (1) enhanced lipase activity due to its unique anatomical location, leading to elevated free fatty acids (FFA) that directly enter the liver via the portal system and accumulate in hepatic adipocytes, exacerbating IR and glucolipid metabolism disorders; and (2) VAT accumulation causing hepatic steatosis through lipid remodeling, mitochondrial dysfunction, reactive oxygen species production, lipid peroxidation, and endoplasmic reticulum stress, ultimately promoting inflammation and progression from non-alcoholic steatohepatitis to fibrosis [13,14].

Another study found that neck circumference correlates with dysglycemia and metabolic syndrome markers and can predict MAFLD risk [15]. However, our results did not support an association between NC and fibrosis, consistent with some previous research. Our multivariate analysis also indicated that NC was not an independent risk factor for fibrosis.

Platelet count emerged as an independent protective factor, with lower PLT associated with higher fibrosis risk. Han et al. [16] found that the PLT/white blood cell ratio significantly decreased in fibrosis patients and served as an independent predictor. Our findings align with this observation. Liu et al. [17] proposed that the liver produces thrombopoietin (TPO), and mitochondrial dysfunction in MAFLD may impair TPO synthesis, leading to reduced PLT. Additionally, while IR alone may not decrease PLT, its presence in MAFLD can trigger PLT reduction, with the degree of reduction correlating with hepatic fat

infiltration [18], consistent with our results.

Recent studies indicate that lncRNA NEAT1 plays an important regulatory role in lipid metabolism [19]. LncRNA NEAT1 is highly expressed in liver tissue of MAFLD rats, and its downregulation can alleviate MAFLD by modulating lipid synthesis via the mTOR/S6K1 signaling pathway [20]. Research also shows that miRNA-140 interacts with lncRNA NEAT1 to enhance its expression and stability, while lncRNA NEAT1 can increase steatosis and worsen MAFLD progression by targeting miRNA-146a-5p to regulate the AMPK/SREBP pathway [21,22]. Our study found significantly elevated peripheral blood lncRNA NEAT1 in T2DM patients with MAFLD, with expression increasing progressively from low- to high-risk fibrosis subgroups. Multivariate analysis identified lncRNA NEAT1 as an independent risk factor for fibrosis. In vitro studies have confirmed that lncRNA NEAT1 can regulate hepatic fibrosis, inflammation, and lipid metabolism by competitively binding miRNA-506 to glioma-associated oncogene homolog 3 (GLI3) [23]. Therefore, we propose that peripheral blood lncRNA NEAT1 expression correlates with fibrosis progression.

MiRNAs are increasingly recognized as important regulators of glucose and lipid metabolism. MiRNA-182-5p has been shown to influence IR and lipid metabolism [24]. Our study found significantly higher miRNA-182-5p in T2DM patients without MAFLD compared to those with MAFLD, consistent with Weale et al. [25] who reported elevated miRNA-182-5p in T2DM and prediabetic subjects. However, Karolina et al. [26] found downregulated miRNA-182-5p in T2DM and suggested it promotes glucose production by targeting forkhead box protein O1 (FOXO1), playing a key role in hepatic IR signaling. Our analysis across fibrosis risk subgroups revealed significantly decreased miRNA-182-5p in the high-risk group. Other researchers have reported reduced miRNA-182-5p in visceral adipose tissue of obese rats and humans, identifying it as a novel negative regulator of adipogenesis [27]. In contrast, studies on schistosomiasis-induced hepatic fibrosis found upregulated miRNA-182 and downregulated FOXO1, which promoted fibroblast proliferation and inhibited apoptosis [28,29]. The relationship between miRNA-182-5p and fibrosis risk in T2DM with MAFLD requires further investigation.

A study on lipopolysaccharide (LPS)-induced acute lung injury found that lncRNA NEAT1 regulates WNT1 inducible signaling pathway protein 1 (WISP1) expression by binding miRNA-182-5p, and that NEAT1 overexpression suppresses alveolar macrophage viability, promoting apoptosis and inflammation via the miRNA-182-5p/WISP1 axis [30]. The role of the lncRNA NEAT1/miRNA-182-5p axis in hepatic fibrosis remains unclear. Our Spearman correlation analysis revealed a negative correlation between these molecules in high-risk fibrosis patients. While animal and cellular experiments are needed for definitive mechanistic insights, our preliminary findings suggest that lncRNA NEAT1 and miRNA-182-5p may play important roles in the pathogenesis of liver fibrosis in T2DM with MAFLD.

This study has several limitations. Many hypoglycemic agents affect MAFLD

and fibrosis through complex mechanisms that are difficult to analyze comprehensively; therefore, we did not evaluate medication effects. Additionally, we used the FIB-4 index rather than histopathological validation to assess fibrosis, which may introduce some error [11].

In conclusion, lncRNA NEAT1 and miRNA-182-5p appear to play important roles in T2DM patients with MAFLD and fibrosis. Elevated lncRNA NEAT1, high VFA, low miRNA-182-5p, and low PLT may represent independent risk factors for liver fibrosis. These findings provide new insights into the mechanisms linking peripheral blood lncRNA NEAT1 and miRNA-182-5p to fibrosis and offer novel directions for preventing fibrosis progression in T2DM patients with MAFLD.

Author Contributions: Jia He and Feng Wei conceived and designed the study. Jia He and Yongping Li implemented the study and drafted the manuscript. Meilan Liu, Yaling Wu, and Longge Shao collected and organized data. Jia He and Meilan Liu performed statistical analysis and created figures. Feng Wei supervised quality control and took overall responsibility for the article.

Conflict of Interest: The authors declare no conflict of interest.

References

[1] JAVEED N, MATVEYENKO AV. Circadian etiology of type 2 diabetes mellitus[J]. Physiology, 2018, 33(2): 138-150. DOI: 10.1152/physiol.00003.2018.

[2] OGURTSOVA K, DA ROCHA FERNANDES JD, HUANG Y, et al. IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040[J]. Diabetes Res Clin Pract, 2017, 128: 40-50. DOI: 10.1016/j.diabres.2017.03.024.

[3] ESLAM M, NEWSOME PN, SARIN SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement[J]. J Hepatol, 2020, 73(1): 202-209. DOI: 10.1016/j.jhep.2020.03.039.

[4] KUMAR S, DUAN QH, WU RX, et al. Pathophysiological communication between hepatocytes and non-parenchymal cells in liver injury from NAFLD to liver fibrosis[J]. Adv Drug Deliv Rev, 2021, 176: 113869. DOI: 10.1016/j.addr.2021.113869.

[5] MA LN, BAJIC VB, ZHANG Z. On the classification of long non-coding RNAs[J]. RNA Biol, 2013, 10(6): 925-933. DOI: 10.4161/rna.24604.

[6] CUI Xueling. Study on the role of lncRNA NEAT1 in the effect of PM2.5 exposure on blood glucose in mice[D]. Shijiazhuang: Hebei Medical University, 2020.

[7] GUTTILLA IK, WHITE BA. Coordinate regulation of FOXO1 by miR-27a, miR-96, and miR-182 in breast cancer cells[J]. J Biol Chem, 2009, 284(35): 23204-23216. DOI: 10.1074/jbc.m109.031427.

[8] Chinese Diabetes Society. Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus (2020 Edition) (Part 1)[J]. Chinese Journal of Practical Internal Medicine, 2021, 41(8): 668-695. DOI: 10.19538/j.nk2021080106.

[9] Chinese Diabetes Society. Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus (2020 Edition) (Part 2)[J]. Chinese Journal of Practical Internal Medicine, 2021, 41(9): 757-784. DOI: 10.19538/j.nk2021090106.

[10] WANG Qi, LIN Zhen, ZHOU Yanhui, et al. Study on the effect of smoking on adverse events in heart failure patients with preserved ejection fraction[J]. Chinese General Practice, 2020, 23(2): 161-165. DOI: 10.12114/j.issn.1007-9572.2019.00.595.

[11] GRAUPERA I, THIELE M, SERRA-BURRIEL M, et al. Low accuracy of FIB-4 and NAFLD fibrosis scores for screening for liver fibrosis in the population[J]. Clin Gastroenterol Hepatol, 2022, 20(11): 2567-2576.e6. DOI: 10.1016/j.cgh.2021.12.034.

[12] YU SJ, KIM W, KIM D, et al. Visceral obesity predicts significant fibrosis in patients with nonalcoholic fatty liver disease[J]. Medicine, 2015, 94(48): e2159. DOI: 10.1097/MD.0000000000002159.

[13] BERGMAN RN, KIM SP, CATALANO KJ, et al. Why visceral fat is bad: mechanisms of the metabolic syndrome[J]. Obesity, 2006, 14(Suppl 1): 16S-19S. DOI: 10.1038/oby.2006.277.

[14] LAFONTAN M, BERLAN M. Do regional differences in adipocyte biology provide new pathophysiological insights?[J]. Trends Pharmacol Sci, 2003, 24(6): 276-283. DOI: 10.1016/S0165-6147(03)00132-9.

[15] FOJAS EGF, BUCKLEY AJ, LESSAN N. Associations between neck circumference and markers of dysglycemia, non-alcoholic fatty liver disease, and dysmetabolism independent of Body Mass Index in an Emirati population[J]. Front Endocrinol, 2022, 13: 929724. DOI: 10.3389/fendo.2022.929724.

[16] HAN Mengran, ZHANG Chenyu, DU Cen, et al. Correlation between platelet/white blood cell ratio and liver fibrosis progression in patients with type 2 diabetes mellitus complicated with non-alcoholic fatty liver disease[J]. Journal of China Medical University, 2022, 51(6): 492-496, 507. DOI: 10.12007/j.issn.0258-4646.2022.06.003.

[17] LIU F, ZHOU H, CAO L, et al. Risk of reduced platelet counts in patients with nonalcoholic fatty liver disease (NAFLD): a prospective cohort study[J]. Lipids Health Dis, 2018, 17(1): 1-7. DOI: 10.1186/s12944-018-0865-7.

[18] LÓPEZ-TRUJILLO MA, OLIVARES-GAZCA JM, CANTERO-FORTIZ Y, et al. Nonalcoholic fatty liver disease and thrombocytopenia III: its association with insulin resistance[J]. Clin Appl Thromb Hemost, 2019, 25: 1076029619888694. DOI: 10.1177/1076029619888694.

[19] BOND CS, FOX AH. Paraspeckles: nuclear bodies built on long noncoding RNA[J]. J Cell Biol, 2009, 186(5): 637-644. DOI: 10.1083/jcb.200906113.

[20] WANG X. Down-regulation of lncRNA-NEAT1 alleviated the non-alcoholic fatty liver disease via mTOR/S6K1 signaling pathway[J]. J Cell Biochem, 2018, 119(2): 1567-1574. DOI: 10.1002/jcb.26317.

[21] SUN YF, SONG Y, LIU CS, et al. LncRNA NEAT1-MicroRNA-140 axis exacerbates nonalcoholic fatty liver through interrupting AMPK/SREBP-1 signaling[J]. Biochem Biophys Res Commun, 2019, 516(2): 584-590. DOI: 10.1016/j.bbrc.2019.06.104.

[22] CHEN X, TAN XR, LI SJ, et al. LncRNA NEAT1 promotes hepatic lipid accumulation via regulating miR-146a-5p/ROCK1 in nonalcoholic fatty liver disease[J]. Life Sci, 2019, 235: 116829. DOI: 10.1016/j.lfs.2019.116829.

[23] JIN SS, LIN XF, ZHENG JZ, et al. lncRNA NEAT1 regulates fibrosis and inflammatory response induced by nonalcoholic fatty liver by regulating miR-506/GLI3[J]. Eur Cytokine Netw, 2019, 30(3): 98-106. DOI: 10.1684/ecn.2019.0432.

[24] CHANDEL R, SAXENA R, DAS A, et al. Association of rno-miR-183-96-182 cluster with diethylnitrosamine induced liver fibrosis in Wistar rats[J]. J Cell Biochem, 2018, 119(5): 4072-4084. DOI: 10.1002/jcb.26583.

[25] WEALE CJ, MATSHAZI DM, DAVIDS SFG, et al. Circulating miR-30a-5p and miR-182-5p in prediabetes and screen-detected diabetes mellitus[J]. Diabetes Metab Syndr Obes, 2020, 13: 5037-5047. DOI: 10.2147/DMSO.S286081.

[26] KAROLINA DS, ARMUGAM A, TAVINTHARAN S, et al. microRNA 144 impairs insulin signaling by inhibiting the expression of insulin receptor substrate 1 in type 2 diabetes mellitus[J]. PLoS One, 2011, 6(8): e22839. DOI: 10.1371/journal.pone.0022839.

[27] DONG MJ, YE YQ, CHEN ZN, et al. microRNA 182 is a novel negative regulator of adipogenesis by targeting CCAAT/enhancer-binding protein A[J]. Obesity, 2020, 28(8): 1467-1476. DOI: 10.1002/oby.22863.

[28] VAN KEUREN-JENSEN KR, MALENICA I, COURTRIGHT AL, et al. microRNA changes in liver tissue associated with fibrosis progression in patients with hepatitis C[J]. Liver Int, 2016, 36(3): 334-343. DOI: 10.1111/liv.12919.

[29] HUANG Y, FAN XX, TAO R, et al. Effect of miR-182 on hepatic fibrosis induced by Schistosomiasis japonica by targeting FOXO1 through PI3K/AKT signaling pathway[J]. J Cell Physiol, 2018, 233(10): 6693-6704. DOI: 10.1002/jcp.26469.

[30] LYU SS, QU XL, QU Y, et al. LncRNA NEAT1 knockdown alleviates lipopolysaccharide-induced acute lung injury by modulation of miR-182-5p/WISP1 axis[J]. Biochem Genet, 2021, 59(6): 1631-1647. DOI: 10.1007/s10528-021-10081-4.

(Received: 2023-04-10; Revised: 2023-07-15)
(Editor: ZOU Lin)

Note: Figure translations are in progress. See original paper for figures.