Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Associations of Leukocyte-Derived Chemotaxin-2 (LECT2) with Insulin Resistance and Metabolic Syndrome in Type 2 Diabetes: A Cross-Sectional Study

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Objective: Leukocyte-derived chemokine-2 (LECT2) is a novel neutrophil chemokine synthesized by the liver. This research aimed to investigate the potential link between LECT2 levels and metabolic syndrome (MetS) as well as insulin resistance (IR) in patients with type 2 diabetes mellitus (T2D). The results could offer fresh perspectives on the diagnosis and therapeutic strategies for T2D and associated metabolic disorders.

Methods: A cross-sectional study was conducted on 148 T2D patients, including 90 with MetS and 58 without MetS. The diagnosis of MetS was based on the standardized guidelines established by the International Diabetes Federation. IR was assessed via HOMA-IR, with a cutoff of ≥2.69. Serum LECT2 levels were measured using ELISA.

Results: In T2D patients, individuals with MetS exhibited significantly higher LECT2 levels than the non-MetS group (1.73±0.31 ng/mL vs 1.55±0.33 ng/mL, $P<0.05$). In addition, LECT2 concentrations were significantly elevated in the IR group compared to the N-IR group (1.75 ±0.33 ng/mL vs 1.61± 0.32ng/mL, $P<0.05$). Higher LECT2 levels were linked to increased metabolic dysfunction, as reflected by elevated FPG, FINS, HOMA-IR, and TG levels. Multivariable logistic regression analysis demonstrated that, after adjusting for multiple confounding factors, LECT2 still exhibits a significant association with the occurrence of MetS (OR=8.48, $P=0.01$).

Conclusion: LECT2 concentrations were elevated in T2D patients combined with MetS and were significantly related to IR. These results indicate that LECT2 could contribute to the pathogenesis of T2D accompanied by MetS, and LECT2 may represent a promising therapeutic target for MetS and its related metabolic disturbances.

Keywords: leukocyte-derived chemokine-2, metabolic syndrome, diabetes mellitus, type 2, insulin resistance

Introduction

Globally, both type 2 diabetes mellitus (T2D) and metabolic syndrome (MetS) have emerged as significant public health challenges. T2D, a chronic metabolic condition marked by insulin resistance (IR) and hyperglycemia, is experiencing growing prevalence worldwide.[1] MetS represents a constellation of interrelated metabolic abnormalities, including atherosclerotic dyslipidemia, central obesity, and hypertension.[2] MetS impacts roughly 20–25% of adults across numerous nations, with prevalence rates showing a consistent upward trend over recent decades.[3] A 2020 Chinese study revealed that 33.38% of the population had MetS.[4] The pathogenesis of MetS includes a variety of genetic and acquired factors, with these elements predominantly manifesting as impaired insulin sensitivity and sustained low-grade inflammation.[5] Extensive research has demonstrated a significant clinical overlap and pathophysiological interconnection between T2D and MetS. These conditions share common underlying mechanisms, particularly IR, and exhibit

Received: 12 March 2025
Accepted: 27 June 2025
Published: 4 July 2025

overlapping risk factors, with obesity being a prominent contributor to their pathogenesis. Clinical evidence indicates that patients with concurrent T2D and MetS face a compounded risk profile, demonstrating not only elevated individual disease risks but also an incremental increase in morbidity with each additional MetS component, compared to non-diabetic individuals.[6,7] Therefore, exploring the pathogenesis and risk factors for patients with both T2D and MetS is beneficial not only for the prevention and control of T2D but also for mitigating the risk of adverse outcomes of metabolic diseases in this population.

Hepatic cytokines, analogous to adipokines and myocytokines, are primarily liver-originated proteins that modulate inflammatory responses, glucose homeostasis, and lipid regulation.[8] As a member of the peptidase M23 family, the 16 kDa protein leukocyte-derived chemokine 2 (LECT2) is primarily secreted by hepatic cells and encoded by its specific gene locus in humans.[9] It has been found that LECT2 can regulate the immune and inflammatory responses of the body in a paracrine manner and is implicated in numerous diseases, including sepsis,[10] hepatitis,[11] arthritis,[12] and hepatocellular carcinoma.[13] Emerging evidence indicates that LECT2 could represent a novel biomarker for various metabolic disorders, particularly IR,[14] obesity,[14] dyslipidemia,[14] atherosclerosis,[15] and other diseases. LECT2 can be used as a potential disease marker for metabolism-related diseases, including obesity,[14] diabetes mellitus,[16] and non-alcoholic fatty liver disease (NAFLD).[17] Chronic inflammation serves as a unifying pathophysiological element among these disease states.[18–23] Thus, it is necessary to further investigate more roles of LECT2, a versatile liver-derived factor linked to chemotaxis, inflammation, and immune regulation in metabolism-related diseases. Furthermore, accumulating evidence indicates significant correlations between LECT2 levels and metabolic indicators across multiple clinical studies.[14,16,24,25] A study of obese and normal-weight Korean women showed that LECT2 mRNA in adipose tissue and LECT2 levels were significantly elevated in obese women and correlated with metabolic parameters, such as body mass index (BMI), insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and triglycerides(TG).[14] Lan et al[24] report that LECT2 was positively associated with HOMA-IR and hemoglobin A1c (HbA1c) while showing inverse associations with insulin sensitivity indices. As reported in a cohort of 143 Japanese men, those diagnosed with MetS demonstrated significantly increased circulating LECT2 levels relative to the controls; individuals with dyslipidemia exhibited elevated LECT2 levels compared to those without.[25] In addition, the research reaffirmed a strong positive link between LECT2 levels and BMI, alanine aminotransferase (ALT), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), TG, fasting insulin (FINS), and HOMA-IR levels.[25] What's more, in individuals newly diagnosed with T2D, a study indicated a notable link between LECT2 and fasting glucose (FPG), FINS, HOMA-IR, HbA1c, TG, HDL-C, and ALT levels.[16] The studies outlined previously indicate a robust link between LECT2 and metabolic disorders. A recent study found that LECT2 expression within metabolic organs of mice responds to a high-fat diet and genetic leptin deficiency.[26] In adipocytes, LECT2 can inhibit insulin-stimulated Akt phosphorylation; furthermore, LECT2 modulates adiponectin (ADIPOQ) expression downward and leptin (LEP) expression upward via a CD209-dependent manner.[27] In conclusion, LECT2 may be a potential biomarker for detecting metabolic disorders in humans from both physiological and clinical perspectives.

No studies have examined the link between LECT2, a novel hepatocyte factor, and MetS in individuals with T2D. Therefore, this study aimed to investigate the relationship between LECT2 levels and MetS as well as IR in T2D patients, so as to determine whether LECT2 serves as an independent risk factor for MetS development in the T2D population and to explore the related potential mechanisms, with a view to providing new ideas for the diagnosis and treatment of related diseases.

Materials and Methods

Subjects

This cross-sectional study included T2D patients admitted to the Department of Endocrinology, Qingpu Branch, Zhongshan Hospital, Affiliated Hospital of Fudan University, from July 2022 to February 2023. The diagnosis criteria of T2D according to the 2025 American Diabetes Association standards.[1] The study has been approved by the Ethics Committee of Qingpu Branch of Zhongshan Hospital Affiliated with Fudan University (Ethics number: Qingyi 2023–74). All participants or their legal representatives gave informed consent. This study adheres to the

World Medical Association's Helsinki Declaration. We excluded subjects who met the following criteria: acute illness; malignancy; history of inflammation potentially influencing results; employment of drugs capable of altering the inflammation within six months, including corticosteroids and NSAIDs; hepatic malignancy; acute liver or renal illness; refusal to sign the written informed consent.

MetS was defined and diagnosed according to criteria established by the Joint Transition Statement (JIS) of the International Diabetes Federation Epidemic Prevention Working Group.[3] The criteria require the presence of three or more of the following components: 1) Central obesity: waist circumference (WC) ≥85 cm in men and ≥80 cm in women, 2) hypertriglyceridemia (fasting plasma TG≥1.7 mmol/L), 3) low HDL-C (fasting HDL-C <1.00 mmol/L in men, <1.30 mmol/L in women), 4) high blood pressure[systolic blood pressure (SBP)≥130mmHg, diastolic blood pressure (DBP) ≥85mmHg, or known treatment for hypertension], and 5) hyperglycemia (FPG ≥5.6 mmol/L, or taking antidiabetic medication, including oral antidiabetic medication or insulin).

Anthropometric and Laboratory Measurements

Patient's demographic and clinical data were obtained via epidemiological surveys or extracted from institutional electronic health records. Height, weight, WC, hip circumference(HC), smoking history (previous or current smoking and smoking cessation or smoking cessation for less than 6 months), drinking history (previous or current drinking and smoking cessation or smoking cessation for less than 6 months), SBP, and DBP were measured. A minimum 5-minute rest period is required prior to BP assessment to ensure measurement accuracy. The patient was seated to measure BP with a suitable cuff and a mercury sphygmomanometer on his/her right arm. The average of triplicate measurements was documented for subsequent examination. Anthropometric assessments, including weight and height, were acquired with a calibrated digital device, adhering to protocols that necessitated the removal of shoes and thick clothes. BMI was calculated by weight(kg)/height(m)^2. WC was recorded above the hips at the narrowest circumference, while HC was taken at the widest hip point. Waist-to-hip ratio (WHR) =WC (cm)/HC (cm) × 100%.

Following a standardized 12-hour overnight fast, all blood samples were gathered in the morning fasting state. Exactly 5 milliliters of venous blood was obtained at dawn the next day and immediately stored at −80°C for subsequent analysis. FINS was measured by an electrochemiluminescence method, while the HbA1c was determined by chromatography. The enzyme colorimetric assay was used to determine ALT, aspartate aminotransferase (AST), fasting blood glucose (FPG), creatinine (Scr), urea nitrogen (BUN), TG, total cholesterol (TC), LDL-C, and HDL-C. Uric acid (UA) was measured via chemiluminescence immunoassay. HOMA-IR, an indicator of IR, was calculated based on FINS and FPG concentrations according to the following formula: HOMA-IR=FINS (μU/mL) × FPG (mmol/L)/22.5.[28] Participants with HOMA-IR values greater than 2.69 were considered to be insulin-resistant.[29] Quantification of serum LECT2 concentrations was performed employing an enzyme-linked immunosorbent assay kit (ELISA) (Biomatik, item number EKN46734). The sensitivity was 0.27 ng/mL, while the intra-group and inter-group variability were less than 10% and 12%, respectively.

Statistical Analysis

Numerical variables are expressed as mean±standard deviation or median and interquartile range, and categorical variables are expressed as N (%). The Shapiro±Wilk test evaluated continuous variable normality. Normally distributed data were presented as mean±standard deviation, with between-group comparisons analyzed via the Student's independent *t*-test (2-tailed). Data that were not normally distributed were expressed as median (interquartile range[25%, 75%]), and comparisons between two groups were made using the Mann–Whitney *U*-test. Parametric variables were assessed via Pearson correlation, while Spearman's method was used for nonparametric data. Multivariate logistic regression evaluated the covariate-adjusted odds ratios (ORs) for the link between LECT2 levels and MetS risk in T2D patients. Data was analyzed using 22.0 software. Charts were created using GraphPad Prism 7.0. *P*-values<0.05 were considered statistically significant.

Results

Comparison of Demographic Characteristics of Research Subjects

Table 1 displays the demographic characteristics of the study subjects. A total of 148 patients with T2D were recruited into this study, consisting of 105 males (71%) and 43 females (29%), with a mean age of 55.55 ± 12.8 years. The median T2D duration was 36 (2, 120) months. Among the participants, 90 patients with T2D (61%) were diagnosed with the MetS, while 58 patients (39%) were classified as non-MetS. T2D patients with MetS showed a significantly higher prevalence of hypertension, WC, HC, WHR, BMI, SBP, and DBP than those with non-MetS ($P < 0.05$). No statistically notable variations were observed in age, duration, percentage of smoking history, or albumin levels among the two groups (Table 1).

Comparison of Biochemical Features of Study Subjects

In T2D patients, compared with the non-MetS group, FPG, FINS, HOMA-IR, ALT, AST, UA, and TG were increased, and HDL-C was decreased in the MetS group ($P < 0.05$) (Table 2). In particular, serum LECT2 levels in the MetS group were significantly higher than in the non-MetS group (1.73±0.31 ng/mL vs 1.55±0.33 ng/mL, $P<0.05$) (Figure 1).

Correlation of LECT2 Levels with Other Parameters

Table 3 presents the correlation analyses conducted on the total study sample, as well as separately for both the MetS and control subsets. Correlation analysis revealed that LECT2 levels were positively correlated with FPG, FINS, HOMA-IR, and TG ($P<0.05$). Furthermore, the MetS group showed a notable positive correlation between LECT2 levels and both FINS and HOMA-IR ($P<0.05$)(Table 3). Interestingly, IR was quantitatively assessed using the HOMA-IR, with a threshold value of ≥2.69 serving as the diagnostic criterion. According to HOMA-IR results, we reclassified all subjects into non-IR group (N-IR, n=47) and IR group (IR, n=101), and the LECT2 level was notably greater in the IR group compared to the N-IR group (1.75±0.33 ng/mL vs 1.61±0.32ng/mL, $P<0.05$) (Figure 2).

The Odds Ratio for MetS According to LECT2 Levels

The multivariate logistic regression revealed a significant link between serum LECT2 and MetS (OR=10.64, 95% CI: 2.55–40.42, $P<0.01$) (Table 4, Model 1). After adjusting for age, sex, BMI, HOMA-IR, and HbA1c (Table 4, Model 2), the association between LECT2 levels and MetS remained significantly correlated (OR = 7.75, 95% CI: 1.88–32.00, $P=0.01$). In addition, after further adjusting for liver and renal function markers (ALT, AST, SCr, BUN, UA), LECT2 remained an independent risk factor for MetS (Table 4, Model 3). The multivariate logistic regression analysis

Table 1 Demographic Characteristics Comparison Between MetS and Non-MetS Groups

	All patients	MetS	Non-MetS
Number (men/women)	148 (105/43)	90 (65/25)	58 (40/18)
Duration (months)	36 (2,120)	80.06 (2,120)	60 (1.75,180)
Age (years)	55.55±12.8	55.43±12.93	55.81±12.7
Smoking (%)	49(33.11)	29(32.22)	20(34.48)
Drinking (%)	17(11.45)	12(13.33)	5(8.62)
Hypertension (%)	55(37)	43(47.78) *	12(20.69)
Waist circumference (cm)	90.64±9.36	94.62±8.34*	84.46±7.23
Hip circumference (cm)	96(91.63, 100)	97(94.75, 102) *	92(88.75, 97)
Waist hip ratio	0.94(0.89, 0.98)	0.96(0.92, 0.99) *	0.9(0.86, 0.95)
BMI (kg/m2)	24.65(22.0, 26.8)	25.99(23.46, 27.86) *	22.76(20.48, 24.61)
Systolic BP (mmHg)	130.03±17.63	132.73±19.22*	125.84±13.96
Diastolic BP (mmHg)	77.53±12.13	79.39±12.22*	74.66±11.49

Notes: *P <0.05 vs Non-MetS.
Abbreviations: BMI, body mass index; BP, blood pressure.

Table 2 Biochemical Characteristics Comparison Between MetS and Non-MetS Groups

	All patients	MetS	Non-MetS
FPG (mmol/l)	8.09(6.6, 9.28)	8.4(7.0, 9.7)*	7.3(6.08, 8.33)
FINS (mIU/l)	6.99(2.09, 8.93)	5.91(2.84, 10.38) *	2.76(1.21, 6.66)
HbAlc (%)	10.81±2.39	11.06±2.29	10.4±2.51
HOMA-IR	1.58(0.7, 3.08)	2.2(1.06, 4.0)*	0.88(0.39, 1.97)
ALT (U/L)	20.5(15, 31.75)	25(17, 33)*	18(13, 24)
AST (U/L)	20(16.25, 25)	23.98(18, 26) *	18(14.75, 22)
SCr (umol/L)	62.14±16.13	62.24±17.52	61.98±13.84
BUN (mmol/L)	5.8(4.8, 7.1)	5.8(4.88, 7.1)	5.6(4.8, 7.15)
UA (umol/L)	305.68±93.73	311.5±96.84*	280.47±83.38
Triglycerides (mmol/l)	1.65(1.06, 2.6)	2.11(1.59,3.23) *	1.0(0.7, 1.48)
Total cholesterol (mmol/l)	4.73±1.27	4.78±1.38	4.65±1.09
HDL cholesterol (mmol/l)	1.02(0.88, 1.22)	0.94(0.82, 1.1)*	1.16(1.03, 1.33)
LDL cholesterol (mmol/l)	2.82±0.95	2.82±0.99	2.83±0.88
LECT2 (ng/mL)	1.66±0.03	1.73±0.31*	1.55±0.33

Notes: *P <0.05 vs Non-MetS.

Abbreviations: FPG, fasting glucose; FINS, fasting insulin; HbA1c, hemoglobin A1c; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, creatinine; BUN, urea nitrogen; UA, Uric acid; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; LECT2, Leukocyte-derived chemokine-2.

demonstrated similar findings after adjusting for potential confounding lipid profiles (TC and HDL-C), which may affect the concentration of LECT2 (Table 4, Model 4).

Discussion

MetS is a growing worldwide concern, significantly impacting both health and life quality, and its prevalence is on the rise worldwide. MetS represents a complex cluster of interconnected metabolic abnormalities comprising IR, abdominal obesity, dyslipidemia, and hypertension.[2] Together, these metabolic disturbances significantly increase susceptibility to both cardiovascular disease and T2D. Furthermore, MetS influences the progression of additional chronic conditions.[30] Therefore, it is crucial to explore new factors associated with MetS and T2D.

Earlier research primarily linked LECT2 to immune and inflammatory functions. Basic research exploring the role of LECT2 in metabolic disorders, such as glucose and lipid metabolism, has expanded significantly recently. However, limited clinical research exists on LECT2 in T2D patients, and there is no conclusive evidence to confirm its function. Therefore, it is necessary to further investigate the role of this liver factor in metabolic diseases. The primary objectives were to analyse the correlations between LECT2 levels and MetS in T2D patients, establish its independence as a risk factor for MetS, and explore the applicability of LECT2 as a therapeutic target.

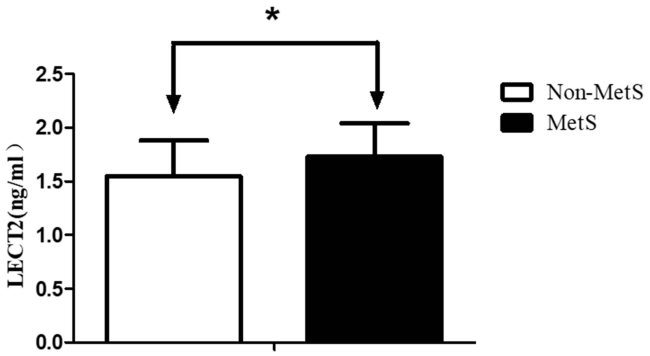

Figure 1 Levels of LECT2 are significantly elevated in patients with MetS than in those without MetS. *Means $P < 0.05$.

https://doi.org/10.2147/DMSO.S527941

Table 3 Correlation Analysis of LECT2 with Anthropometric and Biochemical Parameters

Variables	All Patients (n=148)		MetS (n=90)		Non-MetS (n=58)	
	r	*p*	r	*p*	r	*p*
Duration (months)	0.041	0.625	0.120	0.261	−0.016	0.904
Age (years)	0.148	0.072	0.177	0.095	0.130	0.329
Waist circumference (cm)	0.061	0.459	0.030	0.782	−0.319	0.015*
Hip circumference (cm)	−0.076	0.357	−0.028	0.795	−0.269	0.041*
Waist hip ratio	0.075	0.362	0.077	0.468	−0.161	0.227
BMI (kg/m2)	0.040	0.627	0.007	0.095	−0.173	0.194
Systolic BP (mmHg)	−0.119	0.149	−0.173	0.104	−0.205	0.123
Diastolic BP (mmHg)	−0.014	0.870	−0.155	0.145	0.064	0.633
FPG (mmol/l)	0.197	0.016*	0.095	0.372	0.193	0.146
FINS (mIU/l)	0.169	0.040*	0.243	0.021*	−0.105	0.435
HbAlc (%)	0.051	0.537	−0.016	0.882	0.058	0.666
HOMA-IR	0.219	0.007*	0.245	0.020*	−0.013	0.924
ALT (U/L)	−0.052	0.529	−0.070	0.515	−0.216	0.103
AST (U/L)	0.066	0.427	−0.058	0.588	0.057	0.669
SCr (umol/L)	−0.021	0.797	−0.009	0.934	−0.007	0.959
BUN (mmol/L)	0.059	0.475	0.104	0.332	−0.176	0.190
UA (umol/L)	0.064	0.442	0.014	0.896	−0.008	0.955
Triglycerides (mmol/l)	0.217	0.008*	0.094	0.380	0.056	0.676
Total cholesterol (mmol/l)	0.036	0.662	−0.021	0.843	0.106	0.428
HDL cholesterol (mmol/l)	−0.059	0.473	−0.045	0.676	0.228	0.085
LDL cholesterol (mmol/l)	−0.029	0.724	−0.127	0.234	0.124	0.353

Notes: r denotes correlation coefficient. *Denotes significance at a *P* value of <0.05.

Abbreviations: FPG, fasting glucose; FINS, fasting insulin; BMI, body mass index; BP, blood pressure; HbA1c, hemoglobin A1c; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, creatinine; BUN, urea nitrogen; UA, Uric acid; HOMA-IR, homeostasis model assessment of Insulin resistance; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; LECT2, Leukocyte-derived chemokine-2.

This research assessed differences in LECT2 levels between patients with T2D comorbid with MetS and those without MetS. We analyzed relationships between LECT2 levels and various metabolic parameters while investigating the protein's potential involvement in these metabolic interactions. The main findings were as follows: (1) LECT2 concentrations were elevated in T2D patients combined with MetS compared with non-MetS patients; (2) LECT2 levels were correlated with some metabolic indices; (3) Individuals exhibiting IR demonstrated substantially elevated circulating LECT2 concentrations compared to N-IR patients; (4) After adjusting for potential confounders, elevated LECT2

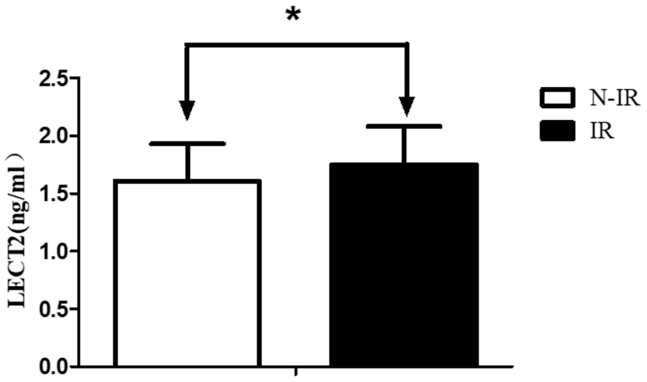

Figure 2 Levels of LECT2 are significantly higher in patients with IR than in those with N-IR. *Means $P < 0.05$.

Table 4 Multivariate Logistic Analysis for the Relationship Between MetS and LECT2

Model Adjusted for LECT2	OR	95% CI	*P*
Model 1	10.64	2.55–40.42	<0.01
Model 2	7.75	1.88–32.00	0.01
Model 3	7.19	1.67–30.90	0.01
Model 4	8.48	1.71–42.08	0.01

Notes: *P* value <0.05 denotes statistical significance across all models. Model 1, adjusted for age and sex, and BMI; Model 2, adjusted for age, sex, BMI, HOMA-IR, HbA1c; Model 3, adjusted for age, sex, BMI, HOMA-IR, HbAlc, ALT, AST, SCr, BUN, UA; Model 4, adjusted for age, sex, BMI, HOMA-IR, HbAlc, ALT, AST, SCr, BUN, UA, total cholesterol, and HDL cholesterol;
Abbreviations: OR, odds ratio; CI, confidence interval; LECT2, Leukocyte-derived chemokine-2.

concentrations remained significantly associated with incident MetS in T2D patients. To our knowledge, this research presents the initial findings linking serum LECT2 concentrations to MetS in T2D patients.

As an important multifunctional protein, the precise pathophysiological mechanisms through which LECT2 contributes to diabetes and related metabolic disorders remain deeply unexplored. Since chronic inflammation and IR significantly contribute to MetS, LECT2 could contribute to MetS development in individuals with diabetes, potentially through modulation of IR. Research indicates that LECT2 contributes to diabetes progression, as its gene deletion enhances tissue glucose uptake.[24] Recent studies indicate a strong association between LECT2 and IR. It has been shown that LECT2 reduces insulin-stimulated AKT phosphorylation by increasing c-Jun N-terminal kinase (JNK) phosphorylation in C2C12 myocytes, thereby enhancing skeletal muscle IR.[24] In addition, LECT2 hinders insulin signaling through decreased phosphorylation of IRS-1 and AKT, and it also decreases glucose uptake triggered by insulin in a CD209-mediated fashion.[31] Our study suggested that LECT2 concentrations positively correlated with FPG, FINS, and HOMA-IR, and were higher in MetS patients than in non-MetS individuals. Furthermore, our study suggests that LECT2 independently increases MetS risk in T2D patients. However, the biological pathways linking LECT2 to IR in MetS are still unclear. Multiple research findings indicate inflammation's potential contribution to the etiology of IR development, defective insulin secretion, and other aspects of disruption of energy homeostasis.[32] LECT2, as a protein with pro-inflammatory functions, influences neutrophil activation and migration to sites of inflammation through its function as a chemokine.[33] The pro-inflammatory and chemotactic properties of LECT2 potentially contribute to IR pathogenesis through as-yet incompletely characterized mechanisms. It should be noted that based on the HOMA-IR results, we reclassified all diabetic subjects into N-IR and IR groups, with LECT2 levels notably elevated in the IR group, further suggesting that LECT2 could contribute to the pathogenesis and progression of diabetes-associated metabolic disorders by affecting IR.

LECT2 is up-regulated in the liver of obese patients by sensing liver fat.[24,34] It can mediate the functional connection between hepatic steatosis and inflammatory responses through macrophage activation in mouse tissues. In addition, it has been found that activation of the hepatic Wnt/β-catenin signaling pathway, a key regulator of hepatic glycolipid metabolism, can enhance serum LECT2 levels.[9] A recent research has revealed that in HFD-induced obese mice and ob/ob mice, baseline LECT2 expression was elevated and markedly increased in metabolic tissues, particularly the liver, along with fat deposits.[26] These studies collectively indicate the intimate connection between LECT2 and lipid metabolism, aligning with our findings that reveal a positive link between LECT2 concentrations and TG levels. What's more, elevated levels of LECT2 are seen in a variety of liver diseases, including chronic hepatitis B, acute liver failure, and metabolic dysfunction-associated steatotic liver disease, suggesting that it is associated with liver injury and inflammation.[35] Experimental investigations demonstrated that genetic ablation of LECT2 attenuated ethanol-induced hepatic damage, whereas transgenic overexpression exacerbated liver injury in murine models.[35] Mechanistic studies have shown that LECT2 promotes reactive oxygen species by interacting with a neutrophil membrane protein, prohibitin 2 (PHB2), which promotes the formation of neutrophil extracellular trapping networks (NETs), which can

further exacerbate hepatic injury.[35] Taking these studies together, we hypothesized that LECT2 could form or aggravate fatty liver by impairing liver function, leading to impaired lipid metabolism, and exacerbating fat accumulation in the liver. Additionally, in other research on mechanisms related to LECT2 and lipid metabolism, Hwang et al[27] even revealed that dipeptidyl peptidase 4 inhibitors ameliorate hepatic steatosis and IR by inhibiting LECT2 expression through AMPK and JNK-dependent pathways. Moreover, scientists have developed an innovative NAFLD/NASH model by leveraging bacterial translocation mechanisms.[36] This model was achieved using genetically modified mice lacking the LECT2 gene.[36] They found that liver steatosis worsened and p38 phosphorylation levels were notably decreased due to LECT2 gene deletion.[36] This researcher also found that under pathological conditions, LECT2 may mitigate lipid buildup and liver macrophage activation, possibly through p38 phosphorylation.[36] Collectively, both basic findings and our clinical results support the involvement of LECT2 in MetS development, primarily through the regulation of lipid metabolic pathways. However, the precise molecular mechanisms underlying LECT2-mediated regulation of lipid metabolism remain incompletely understood, and further mechanistic research is required to clarify this factor's involvement in lipid metabolism dysregulation and related disorders.

As a multifunctional protein, LECT2 exhibits both cytokine-like chemotactic activity and significant regulatory functions in inflammation regulation and immunomodulation.[37] Predisposing systemic inflammation is a critical pathogenic stage preceding the onset of numerous metabolic disorders.[38] Studies have shown that T2D, MetS, and related conditions, including hypertension, prediabetes, fatty liver disease, and obesity, are characterized by a high burden of chronic inflammation.[18–23] Prior research indicates a strong link between LECT2 and numerous metabolic disorders. Our study suggests that serum LECT2 level is an independent risk factor for the development of MetS. Therefore, we suggest that LECT2 may influence the MetS through its potential relationship with inflammatory metabolic factors. Previous research demonstrated that increased LECT2 production in hepatocytes correlates with inflammatory signaling in human hepatic tissue.[37] In 3T3-L1 adipocytes, LECT2 plays a pro-inflammatory role by inducing the phosphorylation of IκB kinase, as well as the release of TNF-α and monocyte chemoattractant protein-1.[31] Furthermore, LECT2 induces the expression of adhesion molecules and pro-inflammatory cytokines via CD209-mediated JNK phosphorylation in HUVECs and THP-1 monocytes.[39,40] In summary, the significance of LECT2 in inflammatory responses is pivotal. The mechanism of LECT2 in the pathogenesis of MetS may partly depend on its pro-inflammatory effect. The precise biochemical mechanisms responsible for these observed effects have not yet been completely characterized, and additional studies are required to deepen insight into these mechanisms.

Several study limitations should be acknowledged. Initially, the research employed a cross-sectional methodology, so the causality between LECT2 and MetS pathogenesis remains unconfirmed. Elevated LECT2 could be a result of metabolic changes rather than a cause. Therefore, prospective studies are necessary to determine its role in the pathogenesis of MetS. Secondly, the study at this single institution involved a limited sample size. Consequently, we could not entirely mitigate the impact of extraneous variables on our findings, potentially diminishing statistical efficacy. If we had studied a larger sample, various non-significant associations might have become statistically significant. Moreover, the research involved Chinese individuals diagnosed with T2D, and its applicability in other national and ethnic populations is unknown. Unfortunately, the absence of a non-diabetic comparator group may have narrowed the significance of our study, and it also limits the breadth of the population to which our study applies. Finally, inflammation is closely associated with the MetS, and LECT2 may participate in MetS pathogenesis through inflammatory pathways in the present study population; however, indicators related to inflammation were not assessed in this study. Similarly, although LECT2 has been shown to be closely associated with MetS and IR, substantial research remains to be conducted on its structure-function relationships and the regulatory mechanisms of various signaling pathways in related diseases.

Conclusions

In conclusion, our research revealed elevated LECT2 levels among T2D patients suffering from MetS, which were associated with IR. Additionally, our findings indicate a significant link between LECT2 and metabolic indicators. Further results revealed a significant link between LECT2 and the occurrence of MetS in individuals with T2D. These findings suggest that LECT2, as a novel metabolic regulator, may contribute to both the initiation and progression of MetS in T2D patients and that this association may be mediated through IR. In addition, these results also provide

a possible link between LECT2 and metabolic diseases. Studies on LECT2 could reveal novel therapeutic targets for the treatment of MetS, and additional extensive anticipatory and empirical research is crucial for investigating the underlying mechanisms in the future.

Ethical Approval

All study procedures complied with the ethical standards of the institutional and/or national research committee and the Declaration of Helsinki.

Acknowledgments

We thank all study participants.

Funding

Supported by Qingpu District Health Committee Project(QWJ2023-24); Ministry of National Education (2023GY006); Qingpu District Three-Year Health Action Plan (SH2019041); Qingpu Branch of Zhongshan Hospital (QY2023-10).

Disclosure

The authors report no conflicts of interest in this work.

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