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Circulating LECT2 levels in newly diagnosed type 2 diabetes mellitus and their association with metabolic parameters

An observational study

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Abstract

Leukocyte cell-derived chemotaxin 2 (LECT2) is a hepatokine expressed in hepatocytes and appears to be involved in energy metabolism. The aim of this study was to determine plasma LECT2 levels in newly diagnosed type 2 diabetic patients and to correlate the results with various metabolic parameters.

A total of 93 newly diagnosed type 2 diabetic patients and 80 age- and sex-matched nondiabetes mellitus ones were enrolled in the study. Plasma LECT2 levels were measured by enzyme-linked immunosorbent assay.

Circulating LECT2 levels were approximately 1.3 times higher in newly diagnosed type 2 diabetic patients than in controls (mean 30.30 vs 23.23 ng/mL, $P < .001$). Correlation analysis showed that LECT2 was negatively associated with high-density lipoprotein-cholesterol (HDL-C) levels in type 2 diabetic patients and obese subjects ($P < .05$). In multiple stepwise regression analysis, HDL-C, HOMA-IR, BMI, FINS, and TG were significantly independent determinants for LECT2 ($P < .05$).

Our study showed that circulating LECT2 concentrations are significantly higher in newly diagnosed type 2 diabetic patients and further elevated in obese type 2 diabetic patients. LECT2 concentrations are significantly negatively associated with HDL-cholesterol levels in newly diagnosed type 2 diabetic patients and obese subjects.

Abbreviations: ALT = alanine transaminase, AMPK = AMP-activated protein kinase, AST = aspartate transaminase, BMI = body mass index, BP = blood pressure, CV = cofficient of variation, FINS = fasting insulin, FPG = fasting plasma glucose, HbA1c = glycosylated hemoglobin, HDL-C = high-density lipoprotein-cholesterol, HOMA-%β = homeostasis model assessment-β cell function, HOMA-IR = homeostasis model assessment-insulin resistance, hs-CRP = high-sensitivity C-reactive protein, IRS-1 = insulin receptor substrates-1, JNK = c-Jun N-terminal kinase, LDL-C = low-density lipoprotein-cholesterol, LECT2 = leukocyte cell-derived chemotaxin 2, mTOR = mammalian target of rapamycin, NDM = nondiabetes mellitus, T2DM = type 2 diabetes mellitus, TC = total Cholesterol, TG = triglycerides, WC = waist circumference, WHO = World Health Organization.

Keywords: glycolipid metabolism, insulin resistance, leukocyte cell-derived chemotaxin 2, type 2 diabetes mellitus

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive debilitating disease, characterized by insulin resistance in relation to dysregulated insulin secretion and loss of β-cell mass.[1] T2DM has become a serious global public health problem, affecting 336 million individuals worldwide.[2] Complications linked to diabetes, including cardiovascular and cerebrovascular events, retinopathy and blindness, nephropathy and renal failure, and neuropathy, have resulted in tremendous economic costs and human health risks. The pathogenesis of type 2 diabetes is greatly complicated and contains the varying degrees of insulin deficiency and insulin resistance resulted from pancreatic β-cell dysfunction. During the last 2 decades, numerous metabolic hormones have been shown to be involved in the pathogenesis of type 2 diabetes. Moreover, the molecular mechanisms of insulin resistance appear to be affected by the aberrant secretion of organokines (e.g., adipokines from adipose tissue and myokines from skeletal muscle) through autocrine/paracrine and endocrine pathways.[3] Analogous to adipokines and myokines, liver-derived proteins that are defined as hepatokines, significantly regulate glucose and lipid metabolism in the pathogenesis of insulin resistance and T2DM.[4]

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Leukocyte cell-derived chemotaxin 2 (LECT2) is a 16-kD pleiotropy protein which was originally identified as a neutrophil chemotactic factor.[5] LECT2 (encoded by human Lect2 gene) is expressed predominantly in human adult and fetal hepatocytes and is secreted into the bloodstream.[6] The early studies have reported that LECT2 might function in immune and inflammatory responses such as hepatitis,[7] arthritis,[8] and antihepatocarcinogenesis.[9–11] Although accumulating evidence indicates that LECT2 acts as a regulator of inflammatory reactions, few studies have focused on the possible involvement of LECT2 in metabolic disorders. Recently, Lan et al[12] redefined LECT2 as a novel hepatokine linking obesity to skeletal muscle insulin resistance. In this study, experiments on animal and cellular indicated that LECT2 induces insulin resistance in the skeletal muscle by activating c-Jun N-terminal kinase (JNK), which can inhibit the phosphorylation of insulin receptor substrates-1 (IRS-1).[12,13] Meanwhile, Hwang et al[14] revealed that dipeptidyl peptidase 4 inhibitors improve hepatic steatosis as well as insulin resistance through AMP-activated protein kinase (AMPK)- and JNK-dependent inhibition of LECT2 expression. Furthermore, Okumura et al[15] demonstrated that serum LECT2 levels are increased in obesity and fatty liver. These data suggest that LECT2 may be involved in metabolic diseases as an energy-sensing hepatokine. However, the functional role of LECT2 in type 2 diabetes development and lipid metabolism remains unclear. To date, there have been few studies examining the clinical significance of circulating LECT2 levels in metabolic diseases including type 2 diabetes in humans. Therefore, this study aimed to determine circulating LECT2 levels in a large cohort of subjects with type 2 diabetes and in nondiabetic mellitus controls. Moreover, the relationships of anthropometric and metabolic parameters with LECT2 were also investigated.

2. Materials and methods

2.1. Subjects

From January 2016 to December 2016, a total of 173 adult Chinese subjects (90 males and 83 females), aged 18 to 69 years, were recruited consecutively from the Endocrinology and Metabolism Department and the Health Management Section of Zhujiang Hospital. Patients with type 2 diabetes mellitus (T2DM) were screened prospectively at this Department. Ninety-three patients with T2DM were enrolled in the study. Eighty age- and sex-matched nondiabetic mellitus (NDM) controls were selected from a population undergoing an annual physical examination at the Health Management Section. Type 2 diabetic patients were diagnosed according to 1999 World Health Organization diagnostic criteria.[16] The exclusion criteria were as follows: patients being treated with insulin or oral hypoglycemic agents; patients with micro- and macrovascular complications; patients with type 1 diabetes or gestational diabetes; patients taking any drugs known to affect glucose, lipid, or hepatic metabolism; patients with viral hepatitis, cancer, hepatic failure, chronic renal failure on hemodialysis, congestive heart failure, or other known major diseases. Written informed consent was obtained from all subjects. This study protocol was approved by the Institute Ethics Committees of Zhujiang Hospital and followed the ethical principles of the Declaration of Helsinki.

2.2. Anthropometric measurements

The subjects underwent the following comprehensive physical and anthropometric measurements: body weight (kg), height (cm), waist and hip circumferences (cm), and systolic and diastolic blood pressure (mmHg). Weight was measured in light clothing without shoes to the nearest 0.1 kg using a calibrated balance scale. Height was measured to the nearest centimeter using a rigid measuring rod. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined as BMI $\geq$25 kg/m^2 according to Asia-Pacific BMI criteria created by the World Health Organization's (WHO's) Western Pacific Region.[17] Waist circumferences (WCs) (cm) were measured with a nonstretchable tape while the subjects were wearing light clothing. WC (to the nearest 0.1 cm) was measured at the minimum circumference between the rib cage and the iliac crest. Systolic and diastolic blood pressure (BP) was measured using an Omron HEM-907XL Digital sphygmomanometer. An average of 2 BP readings, with 10 minutes apart, was obtained.

2.3. Biochemical measurements

Blood samples were collected after an overnight fast, for the determination of fasting plasma glucose (FPG), insulin level, C-peptide, glycosylated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), high-sensitivity C-reactive protein (hs-CRP), and LECT2 levels. Fasting plasma glucose (FPG) and lipid profiles were measured by enzymatic methods. Fasting insulin (FINS) and C-peptide levels were measured by enzyme-amplied chemiluminescence assays. HbA1c was assessed using an affinity-chromatographic method. Serum uric acid levels were evaluated by the uricase method; ALT and AST were quantitated by kinetic methods (Beckman Coulter Inc., Brea, CA). High sensitivity C-reactive protein (hsCRP) was assayed by particle-enhanced immunoturbidimetric assay. Plasma LECT2 levels were quantified using a commercially available ELISA kit (Ab-Match ASSEMBLY Human LECT2 Kit with Ab-Match UNIVERSAL Kit; Medical & Biological Laboratories, Nagoya, Japan) according to the manufacturer's instructions; the intra-assay coefficient of variation (CV) was 2.6% to 3.2%. ELISA was performed in duplicate, and samples with CV values exceeding 5% were excluded. Insulin resistance was evaluated based on homeostasis model assessment of insulin resistance (HOMA-IR), and pancreatic β-cell function was estimated by homeostasis model assessment of β-cell function (HOMA-%β). HOMA-IR and HOMA-%β were calculated using the following formula: HOMA-IR=FPG (mmol/L) $\times$ FINS (IU/mL)/22.5; HOMA-%β = 20 $\times$ FINS (IU/mL)/[FPG (mmol/L) − 3.5].

2.4. Statistical analysis

All statistical analyses were performed with SPSS version 19.0 (SPSS Inc., Chicago, IL). Normal distribution of the data was tested using the Kolmogorox–Smirnov test. Normally distributed variables were presented as mean ± SD, and non-normally distributed variables as median and interquartile range (25th–75th percentile). Comparisons between groups were performed with analysis of variance (ANOVA) followed by least significant differences tests. Correlations between variables were assessed using Pearson correlation analysis by controlling for the covariates. Multivariate linear regression analyses were conducted to adjust the effects of covariates and identify independent relationships. Receiver-operating characteristic (ROC) curves

Table 1

Clinical and metabolic characteristics of type 2diabetic patients and healthy controls.

Variables	T2DM	NDM	*P*
n	93	80	
Gender (M/F)	49/54	41/39	.850
Age, y	43.14 ± 8.90	41.36 ± 7.79	.168
BMI, kg/m^2	26.75 ± 3.63	25.60 ± 3.73	.041*
WC, cm	89.97 ± 10.66	87.55 ± 11.59	.154
FPG, mmol/L	10.19 ± 3.17	5.03 ± 0.49	<.001*
FINS, mIU/L	11.20 ± 3.32	7.28 ± 2.99	<.001*
C-peptide, μg/L	2.50 (1.92–3.04)	1.59 (1.29–2.11)	<.001*
HbA1c, %	9.90 (7.80–10.80)	5.60 (5.30–5.90)	<.001*
HOMA-IR	4.99 ± 2.05	1.65 ± 0.73	<.001*
HOMA-%β	48.76 ± 42.55	102.43 ± 48.11	<.001*
TC, mmol/L	5.89 ± 1.10	5.49 ± 1.00	.015*
TG, mmol/L)	1.69 (0.95–2.84)	1.47 (1.01–2.06)	.190
LDL-C, mmol/L	3.49 ± 1.04	3.34 ± 0.88	.327
HDL-C, mmol/L	1.08 ± 0.33	1.44 ± 0.33	<.001*
hs-CRP, mg/L	2.30 (1.10–3.30)	0.90 (0.77–1.14)	<.001*
ALT, IU/L	21.00 (17.00–28.00)	18.50 (14.00–32.20)	.007*
AST, IU/L	30.00 (23.00–36.00)	23.00 (19.50–26.00)	<.001*
Creatine, μmol/L	73.68 ± 15.06	78.01 ± 22.59	.147
Uric acid, μmol/L	309.00 (264.00–401.00)	366.50 (310.50–427.50)	.006*
LECT2, ng/mL	30.30 ± 9.64	23.23 ± 5.23	<.001*

ALT = alanine transaminase, AST = aspartate transaminase, BMI = body mass index, FINS = fasting insulin, FPG = fasting plasma glucose, HbA1c = glycosylated hemoglobin, HDL-C = high-density lipoprotein-cholesterol, HOMA-%β = homeostasis model assessment-β cell function, HOMA-IR = homeostasis model assessment-insulin resistance, hs-CRP = high-sensitivity C-reactive protein, LDL-C = low-density lipoprotein-cholesterol, LECT2 = leukocyte cell-derived chemotaxin 2, NDM = nondiabetes mellitus, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TG = triglycerides, WC = waist circumference.
* $P < .05$.

were utilized to evaluate the accuracy of LECT2 and other biomarkers to diagnose diabetes mellitus. Thus, the area under the receiver-operating characteristic curve (AUC) was a summary measure over criteria and cut point choices. Two-tailed *P* values <.05 were considered as statistically significant.

3. Results

3.1. Circulating LECT2 levels were significantly increased in T2DM and obese subjects

A total of 173 age- and sex- matched subjects of NDM (n = 80) and T2DM (n = 93) were enrolled for the study. All subjects were ethnic Han Chinese. As shown in Table 1, there was no significant difference between the 2 groups in baseline data such as sex, age, WC, uric acid, creatinine, TG, and LDL-C levels. However, circulating LECT2 concentrations were approximately 1.3 times higher in T2DM patients than in NDM individuals (mean 30.30 vs 23.23 ng/mL, $P < .001$). And when stratified by BMI, LECT2 levels in obese T2DM subjects were almost 1.4 times higher than values obtained for health NDM subjects (mean 32.90 vs 21.02 ng/mL, $P < .001$; Fig. 1).

3.2. LECT2 was negatively associated with HDL-C levels in T2DM and obese subjects

As was revealed through Pearson's correlations analysis, plasma LECT2 levels were correlated only with WC and HDL-C levels in the NDM group ($P < .05$), after adjustment for age, sex and BMI (Table 2). Meanwhile, plasma LECT2 concentrations were correlated with multiple metabolic parameters, including FINS, HbA1c, HOMA-IR, HOMA-%β, and lipid profiles (TG and HDL-C) in the T2DM group (Table 2). When stratified by BMI, LECT2 was negatively associated with HDL-C levels in patients with T2DM and obese subjects without T2DM ($P < .01$; Fig. 2). Furthermore, HDL-C, HOMA-IR, BMI, FINS, and TG were independent determinants of LECT2 ($P < .05$), as was exhibited by the multiple stepwise regression analysis (the regression equation being $Y_{LECT2} = 12.81 - 6.99X_{HDL\text{-}C} + 1.82X_{HOMA\text{-}IR} + 0.77X_{BMI} - 0.52X_{FINS} + 0.67X_{TG}$).

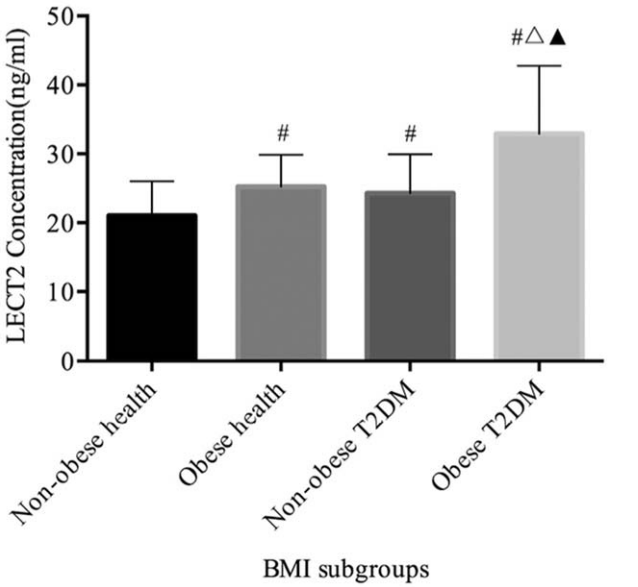

Figure 1. Plasma LECT2 concentrations in BMI subgroups. Data are mean ± SD; versus nonobese health, $^{\#}P < .01$; versus obese health, $^{\Delta}P < .05$; versus nonobese T2DM, $^{\blacktriangle}P < .05$.

Table 2

Correlations between LECT2 levels and various parameters of the study subjects.

	Overall		NDM		T2DM	
Variables	***r***	***P***	***r***	***P***	***r***	***P***
WC, cm	0.011	.885	0.289	.011*	−0.063	.558
FPG, mmol/L	0.546	<.001*	0.150	.194	0.474	<.001*
FINS, mIU/L	0.249	.001*	0.141	.220	0.088	.407
C-peptide, μg/L	0.191	.013*	−0.132	.253	0.021	.846
HbA1c, %	0.475	<.001*	0.092	.425	0.302	.004*
HOMA-IR	0.525	<.001*	0.182	.113	0.446	<.001*
HOMA-%β	−0.434	<.001*	−0.049	.671	−0.368	<.001*
TC, mmol/L	0.067	.387	−0.111	.335	0.021	.841
TG, mmol/L	0.312	<.001*	0.126	.274	0.306	.003*
LDL-C, mmol/L	−0.033	.674	−0.050	.665	−0.099	.353
HDL-C, mmol/L	−0.564	<.001*	−0.422	<.001*	−0.509	<.001*
hs-CRP, mg/L	0.119	.123	−0.074	.521	−0.107	.317
ALT, IU/L	0.130	.092*	0.209	.068	0.037	.727
AST, IU/L	0.210	.006*	0.094	.415	0.145	.174
Creatine, μmol/L	−0.139	.071	−0.102	.375	−0.189	.074
Uric acid, μmol/L	−0.100	.195	−0.070	.543	0.056	.602

nALT = alanine transaminase, AST = aspartate transaminase, FINS = fasting insulin, FPG = fasting plasma glucose, HbA1c = glycosylated hemoglobin, HDL-C = high-density lipoprotein-cholesterol, HOMA-%β = homeostasis model assessment-β cell function, HOMA-IR = homeostasis model assessment-insulin resistance, hs-CRP = high-sensitivity C-reactive protein, LDL-C = low-density lipoprotein-cholesterol, LECT2 = leukocyte cell-derived chemotaxin 2, NDM = nondiabetes mellitus, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TG = triglycerides, WC = waist circumference.

After adjustment on age, sex, and BMI.

* $P < .05$.

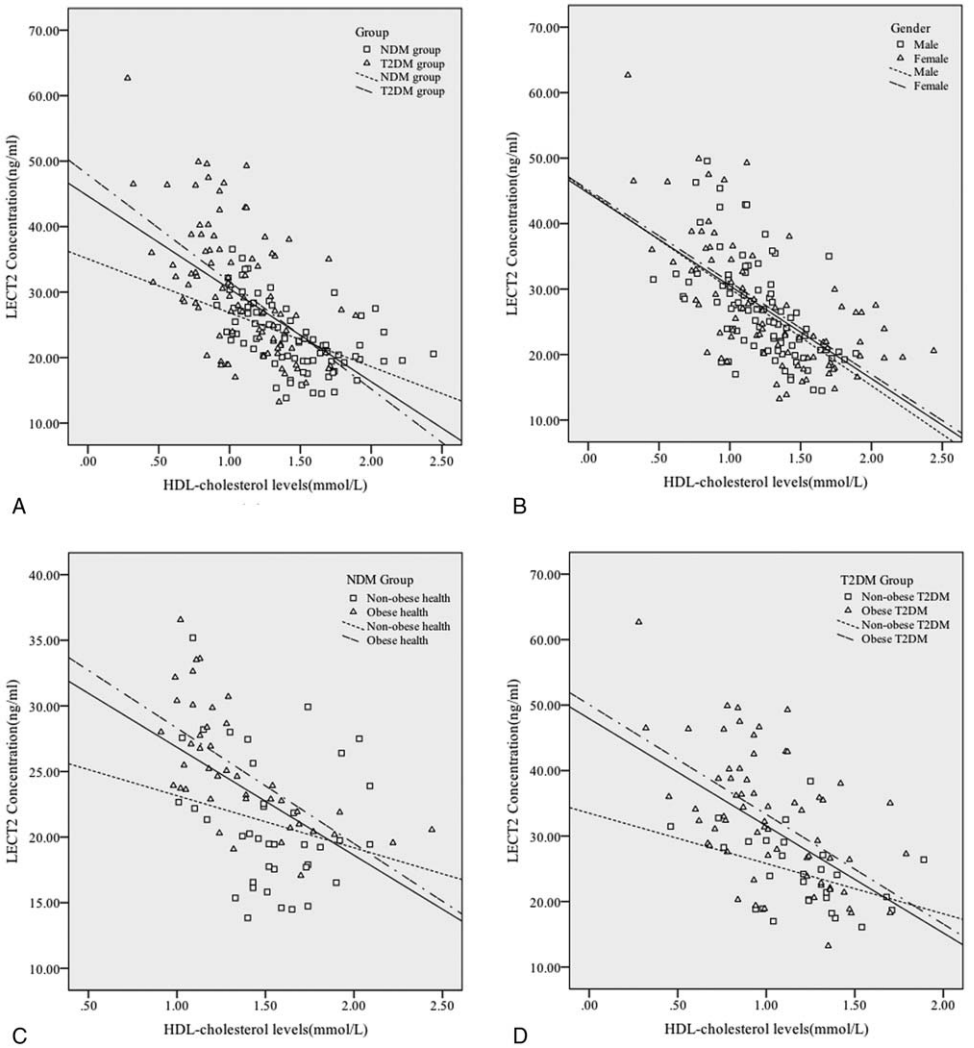

Figure 2. Correlations of plasma LECT2 concentration with HDL-cholesterol levels in each subgroup. (A) Correlations of plasma LECT2 concentration with HDL-cholesterol in NDM and T2DM groups. (B) Correlations of plasma LECT2 concentration with HDL-cholesterol in males and females. (C) Correlations of plasma LECT2 concentration with HDL-cholesterol in NDM group when stratified by BMI. (D) Correlations of plasma LECT2 concentration with HDL-cholesterol in T2DM group when stratified by BMI.

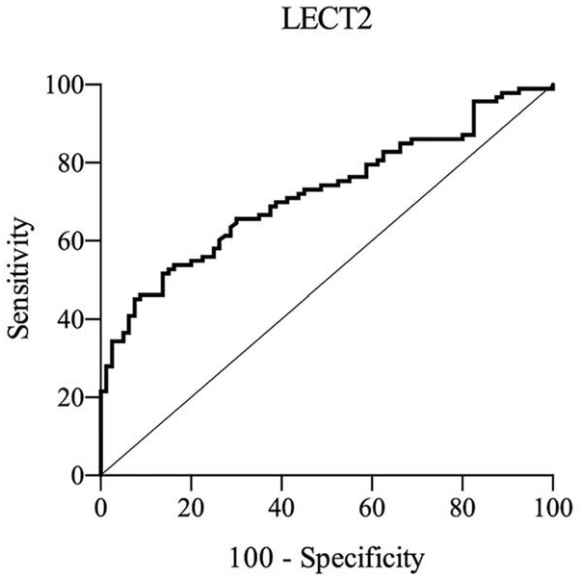

Figure 3. Receiver-operating characteristics (ROC) curves showing the performance of LECT2 concentration in detecting type 2 diabetes mellitus. The receiver-operating characteristic curve analysis. The optimal cutoff point was 28.75 ng/mL. The area under the ROC curve (area between the solid line and *x*-axis) was 0.742 (95% CI, area between the dashed lines and *x*-axis, 0.65–0.78, $P < .01$). The sensitivity and specificity of 51.6% and 86.2%, respectively.

3.3. Performance of LECT2 concentration in detecting T2DM

As revealed by the ROC curve analysis of the diagnostic accuracy of LECT2 level for T2DM, the optimal cutoff point (LECT2 concentration) to predict T2DM was 28.75 ng/mL. Using this cutoff value, diagnostic efficiency for T2DM reached the highest value: the area under the ROC curve was 0.742 (95% CI, 0.65–0.78, $P < .01$), with sensitivity and specificity of 51.6% and 86.2%, respectively (Fig. 3).

4. Discussion

To the best of our knowledge, we described for the first time a higher circulating LECT2 level in T2DM patients than in non-T2DM subjects in the study. We found that LECT2 concentrations were significantly higher in type 2 diabetic patients than in health controls. In addition, we found a negative correlation between LECT2 concentrations and HDL-C levels in patients with type 2 diabetes and obesity.

LECT2 is a novel hepatokine that contributes to the development of skeletal muscle insulin resistance in obesity.[12] As shown above, plasma LECT2 levels were approximately 1.3 times higher in T2DM patients than in NDM individuals; in addition, they were further elevated in obese T2DM subjects. Therefore, the increased LECT2 levels in type 2 diabetic patients seemed to be dependent on obesity. Lan et al[12] found a significant positive correlation between plasma LECT2 levels and BMI and WC. In the same way, Okumura et al[15] showed that plasma LECT2 levels were positively correlated with all 4 major anthropometric measures of obesity: BMI, WC, WHR, and W/Ht. In nondiabetic control subjects, we found a positive correlation between LECT2 levels and WC. Moreover, we showed that LECT2 concentrations were higher in diabetic patients dependently of increased BMI. These data suggest that obesity might be one of the main determinants of plasma LECT2 levels in type 2 diabetic patients, a finding which is in agreement with those of previous studies.[12,15] One might speculate that hyperglycemia per se is associated with increased LECT2 levels because LECT2 was significantly related to HbA1c. Studies evaluating the link between LECT2 levels and glycometabolism have reported conflicting results.[12,15,18,19] The cross-sectional study performed by Tanisawa et al[19] demonstrated that plasma LECT2 levels were not independently associated with HOMA-IR in Japanese men. Okumura et al[15,18] showed that increased serum LECT2 concentrations are not correlated with FPG and HbA1c after adjusting for potential confounders in patients with diabetic retinopathy and healthy participants. In the same vein, Lan et al[12] revealed that LECT2 levels are positively correlated with the HOMA-IR and HbA1c and negatively correlated with insulin sensitivity indices (Matsuda index). Indeed, we found a significantly positive correlation between LECT2 levels and HbA1c in type 2 diabetic patients. One explanation could be the influence of LECT2 on insulin resistance. In addition, plasma LECT2 levels significantly positively correlated with HOMA-IR and negatively correlated with HOMA-%β in type 2 diabetic patients. These results indicate that plasma levels of LECT2 were positively associated with both adiposity and the severity of insulin resistance in type 2 diabetic patients. To our knowledge, however, few clinical markers are available for overnutrition conditions, such as type 2 diabetes and obesity. The ROC curve analysis demonstrated that circulating LECT2 concentration could be a potential biomarker for T2DM. The optimal cutoff value for plasma LECT2 levels for the diagnosis of type 2 diabetes mellitus was 28.75 ng/mL, suggesting that variation in plasma LECT2 levels have clinical significance regardless of extremity.

Our research revealed for the first time that LECT2 concentrations are negatively associated with HDL-C levels in patients with type 2 diabetes and obesity. In addition, we found a positive correlation between LECT2 levels and triglycerides in type 2 diabetic patients. Similarly, Okumura et al[15] also found that LECT2 concentrations show a positive correlation with triglycerides levels and a negative one with HDL-C levels. Besides, a recent cross-sectional study by Tanisawa et al[19] reported that triglycerides and LDL cholesterol levels are independently associated with LECT2 concentrations. These data are in accordance with our study, a fact which reveals the association between lipid profiles with plasma LECT2 levels, suggesting that LECT2 plays a role in the development of dyslipidemia. Furthermore, the experimental study performed by Hwang et al[14] demonstrated that LECT2 increases mammalian target of rapamycin (mTOR) phosphorylation, sterol regulatory element-binding protein (SREBP)-1 cleavage, lipid accumulation, and insulin resistance in HepG2 cells. Because it has been confirmed that activation of liver AMPK enhances fatty acid oxidation and inhibits triglycerides and cholesterol synthesis,[20] LECT2 may play a role in accumulated fat-induced inactivation of liver AMPK, and therefore be associated with dyslipidemia. Multiple stepwise regression analysis further demonstrated that HDL-C, HOMA-IR, BMI, FINS, and TG are significantly independent determinants for LECT2. That suggests that LECT2 might be associated with the dysfunction of glycolipid metabolism. Moreover, Lan et al[12] showed that LECT2 plays a major role in the regulation of insulin resistance under excess caloric conditions, but not under restricted caloric conditions. Therefore, LECT2 may be associated with metabolic disturbances and

unfavorable clinical consequences in individuals with T2DM and obesity.

Several limitations of the present study should be taken into account. First, the sample size was relatively small in this single-center study, which may influence the statistical power. Second, the ethnic group of those enrolled in the present study was Han Chinese; the associations of T2DM and metabolic parameters with plasma LECT2 concentrations should therefore be confirmed in different ethnic groups. Third, we did not perform OGTT in healthy subjects. Although their fasting blood glucose levels were <6.1 mmol/L and their HbA1c levels were <6%, they could possibly be classified in the impaired glucose tolerance group if they performed accordingly to the OGTT. Finally, the limitations include the cross-sectional nature of the present research, which could not confirm the cause–effect relationship between plasma LECT2 and T2DM, as well as obesity.

In conclusion, circulating LECT2 levels were significantly higher in T2DM and obese subjects. In addition, we observed for the first time a negative correlation between plasma LECT2 concentrations and HDL-cholesterol levels in T2DM and obese subjects. It is necessary to proceed further large-scaled prospective studies and the experimental studies with the purpose of exploring the functional roles of LECT2 as a novel hepatokine.

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Investigation: Jianghong Lin. Zhen Zhang.
Project administration: Hong Chen.
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Writing – original draft: Huixian Zeng.
Writing – review & editing: Jia Sun, Zhen Zhang.

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