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ORIGINAL RESEARCH

Nonlinear Relationship Between Low Density Lipoprotein and the Probability of Diabetic Macular Edema

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Purpose: Previous studies simply linearized the relationship between low density lipoprotein (LDL) and diabetic macular edema's (DME) probability, ignoring the possibility of a nonlinear relationship between them. We aimed to investigate the nonlinear relationship between LDL and DME probability in patients with type 2 diabetes mellitus (T2DM).

Patients and methods: The study recruited 431 T2DM patients who attended Guangdong Provincial People's Hospital from December 2017 to November 2018. A multivariate logistic regression model was conducted to evaluate the association between LDL and DME probability. The nonlinear relationship was identified by generalized additive model. Subgroup analyses were performed to assess the consistency of the association in different subgroups.

Results: LDL was positively associated with DME probability (OR=1.60, 95% CI: 1.10~2.34, P=0.0145) after adjusting for covariates. A nonlinear relationship between LDL and DME probability was discovered, with an inflection point for LDL around 4.85 mmol/L (95% CI: 4.18~4.93, P=0.037). The effect sizes and the confidence intervals on the left and right sides of inflection point were 2.17 (1.31 to 3.58) and 0.26 (0.04 to 1.77), respectively. Subgroup analyses revealed other variables had no effect on the association between them.

Conclusion: Our finding suggested LDL was positively correlated with DME probability in T2DM patients. And the relationship between LDL and DME probability was nonlinear. Our findings need to be confirmed by further causal researches.

Keywords: low density lipoprotein, diabetic macular edema, nonlinearity, association

Introduction

Diabetic macular edema (DME) is defined as retinal thickening that approaches or involves macular center due to abnormal intramacular liquid accumulation under diabetic condition.[1] DME is the main cause of visual impairment in patients with type 2 diabetes mellitus (T2DM), with morbidity raging from 1.4% to 5.57%.[2] The prevalence of DME is rising in tandem with the global prevalence of T2DM, which not only has a negative impact on people's quality of life but also causes a significant economic burden on health care budgets.[3] Investigating DME risk factors would benefit in the effective treatment of DME and the reduction of its recurrence rate.

Most researches have proved that hyperlipidemia is one of the risk factors for DME.[4] Increased permeability of the retinal microvasculature leads to outward leakage and deposition of intravascular lipoproteins, resulting in the loss of retinal cell function in the affected areas.[5] The hard exudate in fundus photographs is the compound formed by lipid-filled macrophages and extracellular lipids.[5] Low density lipoprotein (LDL), which accounts for 80–90% of circulating cholesterol, is a key indicator of hyperlipidaemia.[6] LDL primarily transports cholesterol from blood to peripheral tissues,

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where it is eventually eliminated through receptors.[6] Under pathological conditions, LDL tends to be converted to oxidized LDL (OxLDL) in the damaged endothelium, triggering a cascade of vascular events such as endothelial dysfunction and atherosclerosis.[7]

Most current clinical studies on the association between lipoproteins and DME simply linearized their relationship, without considering the nonlinear relationship.[4] However, nonlinear association between exposure and outcome were more common in biomedical research. In such case, a more efficient method was required to deal with nonlinear relationships. Therefore, we conducted a secondary analysis based on the available data from a published paper.[8] In original paper, the author suggested LDL was one of risk factors for DME by using binary logistic regression analysis. While in secondary analysis, a two-piecewise logistics regression model was conducted to identify the nonlinear relationship between LDL and DME probability.

Method

Data Source and Study Population

The data came from the "Dryad" database (https://datadryad.org). This website allows users to free download the raw data from the literature. We cited the related Dryad data package in our paper according to Dryad terms of service [Zhuang, Xuenan et al, Data from: Association of diabetic retinopathy and diabetic macular edema with renal function in southern Chinese patients with type 2 diabetes mellitus: a single-center observational study, Dryad, Dataset, https://doi.org/10.5061/dryad.6kg1sd7]. The original research was a retrospective study that included 431 patients with T2DM who received an ophthalmology consultation in the Department of Endocrinology at Guangdong Provincial People's Hospital from December 2017 to November 2018. The following were the exclusion criteria for the research population: 1) Other ocular diseases such as glaucoma, endophthalmitis, retinal vascular obstruction, age-related macular degeneration, refraction greater than 3.00D and ocular trauma; 2) Previous history of intravitreal injections or renal dialysis; 3) Severe systemic diseases, such as myocardial infarction, cerebral infarction and connective tissue disease; 4) Women in pregnancy or menstrual status. More study specifics could be found in the research completed by Zhuang et al.[8] Zhuang et al declared unequivocally: This study was conducted in accordance with the Helsinki Declaration and was approved by the Research Ethics Committee of Guangdong Provincial People's Hospital (Registration Number: gdrec2016232A).

Variable Source and Definition of DME

Participants clinical information was acquired through electronic medical records. Laboratory tests include liver and kidney function, lipid analysis and urinalysis. Blood and urine samples were taken when patients were fasting before 8:00 a.m. DME was evaluated by a fundus specialist through fundus photography. According to the Early Treatment Diabetic Retinopathy Study Report, DME was defined as a retinal thickness or hard exudate within one optic disc diameter of the macular fovea with fundus manifestations of diabetic retinopathy.[9] The measurement and criteria for each variable were described in detail in the research completed by Zhuang et al.[8]

Statistical Analysis

The participants were divided into two groups based on the presence of DME, and their clinical characteristics were described and compared across groups. Continuous variables with normal distributions were presented as "mean (standard deviation)" with P-values derived from two independent sample *t*-tests, while continuous variables with non-normal distributions were presented as "median (Q1-Q3)" with P-values derived from Mann–Whitney *U*-test. Categorical variables were presented as "sample size (%)" and P-values were derived from $\chi 2$ test. The logistic regression model was conducted to investigate the association between LDL and DME probability. LDL was firstly analyzed as a continuous variable, and then a dichotomous based on the reference interval in clinical practice (0.00–4.14 mmol/L). We presented the unadjusted, minimally adjusted and fully adjusted models in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology recommendations. A covariate would be adjusted when it met the following criteria: 1) Odd ratio (OR) had changed by at least 10% when covariate was included in or excluded from the model;[10] 2) Covariate was associated with both LDL and DME in clinical practice; 3) Covariate was adjusted in previous similar studies.[4] Only one covariate was adjusted when there were congener covariates in the set of adjusted

covariates. In addition, we used a generalized additive model to identify the nonlinear relationship between LDL and DME probability. A two-piecewise logistics regression model would be conducted if a nonlinear relationship was observed. Then the inflection point was determined based on the recursive algorithm, and the 95% confidence interval (CI) of the inflection point was calculated by bootstrap algorithm. The log-likelihood ratio test was applied to compare the one-piecewise regression model with the two-piecewise regression model. P-values for interactional tests were derived from likelihood ratio tests and stratified linear regression models for subgroup analyses. In all analyses, P-values less than 0.05 (two-sided) were considered statistically significant. EmpowerStats version 4.2 (http://www.empowerstats.net/analysis/, X&Y Solutions Software, Boston, MA, USA) and the R language package version 4.2.0 (http://www.R-project.org/, The R Foundation) were used for statistical analysis.

Results

The Characteristic of Participants

Table 1 shows the baseline characteristics of the study population. 431 patients (244 men and 187 women) participated in the study, with a mean age of 59.08 years and a median DM duration of 10 years (range: 1–31 years). There were 164 diabetes retinopathy patients with a probability of 38.05%. DME was found in 56 patients, with a probability of 12.99%

Table 1 Characteristics of the Study Participants

Variable	Overall Population (n=431)	Without DME (n=375)	With DME (n=56)	P-value
Age (years)*	59.08 (13.37)	59.16 (13.60)	58.54 (11.76)	0.744
Male sex, n (%)‡	244 (56.61%)	214 (57.07%)	30 (53.57%)	0.623
DM duration (years)†	10.00 (2.25–15.00)	9.00 (2.00–14.75)	10.00 (8.00–16.00)	0.008
SBP (mmHg)†	136.00 (125.00–152.00)	136.00 (124.00–150.00)	149.00 (126.75–163.75)	0.005
DBP (mmHg)*	79.81 (11.65)	79.61 (11.48)	81.15 (12.79)	0.364
Hypertension, n (%)‡	211 (48.96%)	178 (47.47%)	33 (58.93%)	0.109
Serum albumin (g/L)†	37.80 (35.30–40.25)	38.20 (35.68–40.40)	35.60 (30.30–38.55)	<0.001
HbA1c (%)†	9.45 (7.90–11.28)	9.40 (7.90–11.28)	9.50 (8.15–11.22)	0.946
ALT (U/L)†	18.00 (13.00–26.00)	19.00 (14.00–27.00)	13.50 (11.00–20.25)	<0.001
AST (U/L)†	19.00 (15.00–24.00)	19.00 (15.00–24.00)	16.50 (13.75–22.25)	0.033
Acetylcholinesterase (U/L)*	8378.38 (2019.98)	8394.62 (2090.93)	8115.58 (1814.82)	0.348
D-dimer (ug/L)†	350.00 (270.00–560.00)	350.00 (270.00–520.00)	490.00 (300.00–892.50)	0.002
TC (mmol/L)†	4.90 (3.96–5.80)	4.80 (3.90–5.70)	5.70 (4.50–6.44)	<0.001
TG (mmol/L)†	1.52 (1.05–2.27)	1.51 (1.05–2.22)	1.75 (1.09–2.96)	0.449
HDL (mmol/L)†	0.98 (0.82–1.16)	0.98 (0.82–1.13)	1.06 (0.87–1.28)	0.021
LDL (mmol/L)*	3.20 (0.99)	3.15 (0.96)	3.58 (1.01)	0.002
NEFA (mmol/L)†	0.34 (0.21–0.50)	0.37 (0.25–0.52)	0.29 (0.15–0.44)	0.009
Lipoprotein A (mg/L)†	112.00 (57.00–243.00)	116.00 (65.00–244.00)	164.00 (102.75–345.50)	0.012
Apolipoprotein A (g/L)†	1.12 (0.97–1.27)	1.15 (1.01–1.27)	1.11 (1.01–1.36)	0.306
Apolipoprotein B (g/L)†	0.90 (0.71–1.12)	0.92 (0.74–1.11)	1.04 (0.90–1.23)	0.003
BUN (mmol/L)†	5.60 (4.47–7.35)	5.50 (4.41–6.91)	7.58 (5.35–11.65)	<0.001
Serum creatinine (umol/L)†	73.85 (62.63–90.03)	72.70 (61.65–88.15)	83.90 (70.40–128.93)	<0.001
Urinary albumin (mg/L)†	8.85 (3.78–37.59)	8.18 (3.79–27.27)	75.95 (22.23–622.22)	<0.001
Urinary creatinine (umol/L)†	7.00 (4.43–11.34)	7.54 (4.82–11.99)	4.96 (3.50–6.63)	<0.001
UACR (mg/g)†	9.88 (4.04–52.75)	8.34 (3.85–31.40)	111.90 (31.20–938.46)	<0.001
eGFR (mL/min/1.73 m²)†	88.84 (68.50–101.52)	90.26 (71.88–101.73)	64.78 (32.84–91.07)	<0.001
UACR Stage (≥ Stage 3), n (%)‡	63 (14.62%)	36 (9.60%)	27 (48.21%)	<0.001
CKD Stage (≥ Stage 3), n (%)‡	83 (19.26%)	57 (15.20%)	26 (46.43%)	<0.001
With DR, n (%)‡	162 (38.48%)	108 (28.80%)	56 (100.00%)	<0.001

Notes: *For continuous variables with normal distribution, values were presented as Mean (SD); †For continuous variables with abnormal distribution, values were presented as Median (Q1-Q3); ‡For categorical variable, values were presented as N(%).

Abbreviations: DME, diabetic macular edema; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; ALT, alanine aminotransferase; AST, aspartate transaminase; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low density lipoprotein; NEFA, non-esterified fatty acid; BUN, blood urea nitrogen; UACR, urine albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; DR, diabetic retinopathy.

in 431 participants and 34.15% in 164 diabetes retinopathy patients. Participants with DME had a longer DM duration, lower levels of serum albumin, alanine aminotransferase and aspartate transaminase, higher blood urea nitrogen and D-dimer levels, higher serum level of LDL and higher probability of hypertension, dyslipidemia and renal insufficiency compared to those without DME (Table 1).

The Relationship Between LDL and DME Probability

Logistic regression model was applied to observe the relationship between LDL and DME probability. LDL was positively associated with DME probability in the crude model (OR=1.56, 95% CI: 1.17–2.08, P=0.0023). And there was no significant change in the results in the minimally adjusted model (OR=1.63, 95% CI: 1.20–2.20, P=0.0016). In the fully adjusted model, LDL was still positively correlated with DME probability (OR=1.60, 95% CI: 1.10~2.34, P=0.0145. Table 2). LDL was then analyzed as a dichotomous variable based on the reference interval in clinical practice. The OR in higher LDL group (LDL>4.14 mmol/L) was 3.30 (95% CI: 1.33–8.19, p=0.0101) compared with lower LDL group (LDL≤ 4.14 mmol/L) in the fully adjusted model, implying a 230% increase in DME risk in higher LDL group (Table 2).

The Analysis of Nonlinear Relationship

The generalized additive model was applied to demonstrate the relationship between LDL and DME probability, and a nonlinear relationship was observed (Figure 1). The inflection point was at 4.85 mmol/L (95% CI: 4.18~4.93, P for likelihood: 0.037) according to the fully adjusted two-piecewise logistics regression model (Table 3). On the left of inflection point, LDL was positively associated with DME probability (OR=2.17, 95% CI: 1.31 to 3.58, p=0.0024), while no association was found on the right of inflection point (OR=0.26, 95% CI: 0.04 to 1.77, P=0.1677 Table 3).

The Results of Subgroup Analyses

Subgroup analyses were conducted to explore factors that might modify the association between LDL and the probability of DME (Table 4). Age, gender, DM duration, hypertension, serum albumin level, urine albumin-to-creatinine ratio stage and chronic kidney disease stage were chosen as stratification factors. The results revealed that none of the above stratification factors affected the association between LDL and the probability of DME (Table 4).

Discussion

Our findings indicated a nonlinear relationship with an inflection point between LDL and DME probability in patients with T2DM. And on the left and right sides of the inflection point, the relationship between LDL and DME probability was observed differently. Subgroup analyses suggested a stable relationship between the LDL and DME probability.

Most previous clinical studies have confirmed LDL as a risk factor for DME probability in patients with T2DM. In the original study, Zhuang et al discovered that LDL was a one of risk factors for DME probability (OR=1.46) in

Table 2 The Linear Relationship Between LDL and DME Probability in Different Models

Variable	Crude Model	Model I	Model II
LDL	1.56 (1.17, 2.08) 0.0023	1.63 (1.20, 2.20) 0.0016	1.60 (1.10, 2.34) 0.0145
LDL (Binary)			
≤4.14	Reference	Reference	Reference
>4.14	3.00 (1.59, 5.67) 0.0007	3.14 (1.62, 6.09) 0.0007	3.30 (1.33, 8.19) 0.0101

Notes: The models were presented as OR (95% CI), P-value. Crude model: We did not adjust for other covariates. Model I: Adjusted for age, sex and diabetes mellitus duration. Model II: Adjusted for age, sex, serum albumin, hypertension, hemoglobin A1c, alanine aminotransferase, D-dimer, blood urea nitrogen, urine albumin-to-creatinine ratio stage, diabetic retinopathy stage.

Abbreviations: LDL, low density lipoprotein; DME, diabetic macular edema; OR, odd ratio; CI, confidence interval.

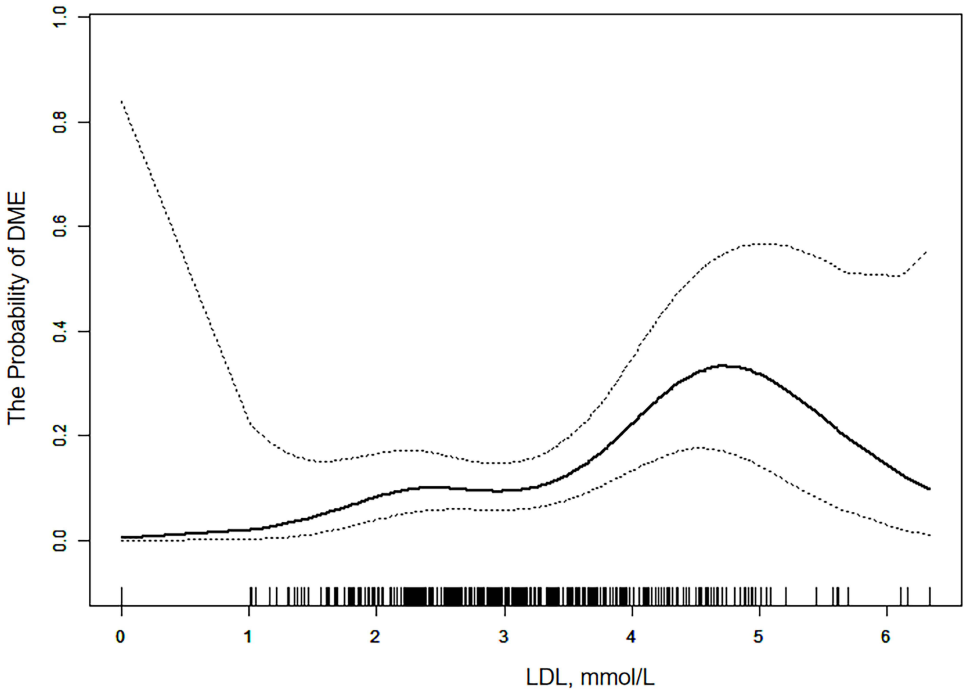

Figure 1 The relationship between LDL and DME probability.
Notes: A nonlinear relationship between them was detected after adjusting for age, sex, serum albumin, hypertension, hemoglobin A1c, alanine aminotransferase, D-dimer, blood urea nitrogen, urine albumin-to-creatinine ratio stage, diabetic retinopathy stage.

southern Chinese patients with T2DM through the multivariate logistic regression model.[8] The same conclusion was drawn (OR=1.358) through the multivariate logistic regression model in a cross-sectional study of 1382 southern Indian patients with T2DM.[11] In a prospective study of 500 Australian patients with T2DM, LDL was still found to be a risk factor for DME probability (OR=1.55) after adjusting for age, gender, duration of diabetes, hemoglobin A1c, systolic blood pressure, body mass index, and use of hypoglycemic drugs, insulin, and lipid-lowering agents.[12] Other studies have also reported a positive association between LDL and DME probability.[13,14] The findings of the preceding studies were largely consistent with our results. However, they ignored the nonlinear relationship between LDL and DME probability due to the assumption of linear relationship and the application of the linear regression model.

LDL was found to be significantly associated with fundus manifestations in DME, such as exudation, macular thickness and so on, in addition to the probability of DME. A few cross-sectional studies reported positive associations

Table 3 The Nonlinear Relationship Between LDL and DME Probability in Adjusted Model

	Adjusted Model
Model I: One line effect	1.60 (1.10, 2.34) 0.0145
Model II: Two-piecewise effect	
Inflection Point (95% CI)	4.85 (4.18, 4.93)
<4.85	2.17 (1.31, 3.58) 0.0024
≥4.85	0.26 (0.04, 1.77) 0.1677
P for likelihood	0.037

Notes: The model was presented as OR (95% CI), P-value. Adjusted model: we adjusted age, sex, serum albumin, hypertension, hemoglobin A1c, alanine aminotransferase, D-dimer, blood urea nitrogen, urine albumin-to-creatinine ratio stage, diabetic retinopathy stage.
Abbreviations: LDL, low density lipoprotein; DME, diabetic macular edema; OR, odd ratio; CI, confidence interval.

Table 4 The Relationship Between LDL and DME Probability in Prespecified and Exploratory Subgroups

Characteristic	No. of Participants	Adjusted Model	P for Interaction
Age (years)			0.6154
< 60	207	1.55 (0.82, 2.93) 0.1728	
≥ 60	220	1.74 (1.05, 2.88) 0.0326	
Gender			0.4092
Male	244	1.27 (0.74, 2.21) 0.3869	
Female	185	2.26 (1.20, 4.26) 0.0115	
DM duration (years)			0.5265
< 10	211	1.32 (0.63, 2.77) 0.4638	
≥ 10	217	1.70 (1.11, 2.61) 0.0146	
Hypertension			0.9859
No	219	1.43 (0.78, 2.63) 0.2420	
Yes	210	1.91 (1.08, 3.36) 0.0253	
Serum albumin (g/L)			0.6487
< 40	301	1.63 (1.09, 2.44) 0.0173	
≥ 40	124	0.86 (0.14, 5.12) 0.8642	
UACR Stage			0.5135
< Stage 3	367	1.43 (0.89, 2.29) 0.1369	
≥ Stage 3	62	2.03 (1.00, 4.10) 0.0489	
CKD Stage			0.9662
< Stage 3	347	1.60 (1.00, 2.59) 0.0522	
≥ Stage 3	82	1.75 (0.85, 3.57) 0.1261	

Notes: The models were presented as OR (95% CI), P-value. The adjusted model was adjusted for age, sex, serum albumin, hypertension, hemoglobin A1c, alanine aminotransferase, D-dimer, blood urea nitrogen, urine albumin-to-creatinine ratio stage, diabetic retinopathy stage. And in each subgroup, the model was not adjusted for the stratification variable.

Abbreviations: LDL, low density lipoprotein; DME, diabetic macular edema; DM, diabetes mellitus; UACR, urine albumin-to-creatinine ratio; CKD, chronic kidney disease; OR, odd ratio; CI, confidence interval.

between LDL and central macular thickness, central macular volume, and total hard exudate area in patients with T2DM, respectively.[15–17] Kameda et al discovered that diabetic patients with higher baseline LDL levels had a more progressive hard exudate, severer macular edema and a worse visual prognosis in the future.[18] It should be noted that these studies had a potential statistical limitation — The preconceived notion of a linear relationship between exposure and outcome.

The nonlinear relationship between LDL and DME probability observed in this secondary analysis required careful consideration and interpretation. Table S1 shows that when compared with the low LDL group (LDL<4.85 mmol/L), participants in the high LDL group (LDL≥4.85 mmol/L) have higher lipoprotein levels. Those with higher lipoprotein levels were more likely to use lipid-lowering drugs. Furthermore, some researches have indicated that taking lipid-lowering drugs may reduce the risk of DME. Chung et al discovered that taking statins for hyperlipidemia reduced the risk of DME (OR=0.33).[19] Some randomized controlled trials demonstrated that the using of Fenofi brate (a lipid-lowering drug) improved symptoms in patients with DME.[20,21] In addition, participants in the high LDL group (LDL ≥4.85 mmol/L) have generally poorer kidney function (Table S1). And patients with impaired kidney function tended to require haemodialysis. Some studies reported a significant improvement in DME symptoms after haemodialysis,[22–24] which could be explained by the fact that haemodialysis improves the volume load and fluid circulation of the entire body, including the eyes. The characteristics and medical behavioral tendencies of participants in high LDL group may contribute to the weakened association between LDL and DME probability under high serum LDL levels.

The mechanisms by which high LDL levels caused the development and progression of DME were not fully understood. It had been postulated that high LDL levels played an important role in the breakdown of the blood retinal barrier, resulting in the occurrence of DME.[3,25] High LDL was more likely to be oxidized and transform into Oxidized

LDL (OxLDL) under oxidative stress condition such as hyperglycemia.[26] OxLDL increased ROS production by activating the Wnt pathway in a dose-dependent manner, resulting in more OxLDL production that ultimately aged retinal pigment epithelial (RPE) and inhibited their differentiation.[25] Moreover, OxLDL activated inflammatory factors such as tumor necrosis factor-α and vascular endothelial growth factor,[27] and caused the dysfunction of ZO-1 proteins (a tight junction protein between RPE) through the mediation of Wnt pathway, which increased RPE permeability and destructed the outer blood-retinal barrier (BRB).[25] OxLDL also activated the nuclear factor-kappa B pathway in vascular endothelia via lectin-like Ox-LDL receptor-1, promoting inflammatory factors expression and endothelial damage.[28] Meanwhile, OxLDL increased the expression of caspases[29] and Fas receptors,[30] inducing endothelial apoptosis and eventually destroying the inner BRB, which is composed of retinal vascular endothelium.[31] The destruction of the inner and outer BRB was a key mechanism in the evolution of DME.[3] Disruption of the inner BRB increased vascular permeability and rupture, leading to the increased leakage of plasma, lipoproteins and red blood cells, which manifested clinically as edema, exudation and haemorrhage.[32] While disruption of the outer BRB increased the leakage and accumulation of extracellular fluid, as well as the difficulty in removal of fluid accumulation, resulting in persistent macular edema.[33]

It should be noted that our analysis had some advantages over previous similar studies. We used a generalized additive model to identify the nonlinear relationship between LDL and DME probability. And in order to calculate the inflection point, we conducted a two-piecewise logistics regression model and the recursive algorithm. This was the highlight of our analysis. In addition, the subgroup analyses were performed to explore the factors that may influence the relationship between LDL and DME probability, which was not previously available in similar studies. However, potential limitations should be considered when interpreting the results of our study. Firstly, since our study only included southern Chinese patients with T2DM, our conclusion should be interpreted with caution in patients with macular edema caused by other diseases. Secondly, smoking, BMI and carbohydrate-restricted diet may affect the LDL level, but the data did not include the relative information. Thus, whether these factors affect the association between LDL and DME remind unknown. Thirdly, as the original research was a cross-sectional study of disease prevalence rather than incidence, the level of LDL that preceded the DME observed was uncertain. Lastly, our analysis tested association instead of causation.

In conclusion, based on our results, there was a nonlinear relationship and saturation effect between the LDL and DME probability, with an inflection with an inflection point of 4.85 mmol/L. Higher LDL levels may indicate a higher risk of DME. Paying attention to LDL levels in patients with T2DM may help to alert us for DME screening, which would benefit in early diagnosis and early treatment, avoiding the worse visual prognosis due to delayed treatment. Further prospective studies with large samples were required to determine whether changes in LDL level affected the incidence of DME and external validation of their nonlinear relationship.

Data Sharing Statement

The dataset was collected by Zhuang et al and is now available on Dryad (via: https://doi.org/10.5061/dryad.6kg1sd7). The datasets generated or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was performed according to the Declaration of the Helsinki and approved by the institutional review board of Guangdong Provincial People's Hospital (registration number: gdrec2016232A). Since the original study was a retrospective cross-sectional study and the data were anonymous, the requirement for informed consent was therefore waived by institutional review board of Guangdong Provincial People's Hospital.

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Disclosure

The authors declare that they have no competing interests.

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