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Association between macular hard exudates and blood lipids in non-proliferative diabetic retinopathy

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非增殖期糖尿病视网膜病变患者黄斑区硬性渗出与血脂的关系

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摘要

目的:探讨2型糖尿病(T2DM)非增殖期糖尿病视网膜病变(NPDR)患者血脂异常与黄斑区硬性渗出(HEs)的相关性。

方法:选取2021年1月至2023年12月于我院眼科门诊就诊的NPDR患者,根据HEs的严重程度将其分为三组:A组(无或少量HEs)、B组(明确HEs)和C组(显著HEs)。常规检测总胆固醇(TC)、甘油三酯(TG)、低密度脂蛋白胆固醇(LDL-C)、高密度脂蛋白胆固醇(HDL-C)、脂蛋白(a)[Lp(a)]及其他血脂相关指标水平,并分析上述指标与HEs的相关性。

结果:A组(24眼)男9例,女15例,平均年龄54.71±6.15岁;B组(52眼)男20例,女32例,平均年龄55.08±6.27岁;C组(14眼)男9例,女5例,平均年龄53.93±6.08岁。C组TC、TG、LDL-C及Lp(a)水平最高,B组次之,A组最低,组间差异均有统计学意义($P<0.001$)。三组间空腹血糖(FPG)、糖化血红蛋白(HbA1c)、血肌酐(Cr)及HDL-C水平差异均无统计学意义($P>0.05$)。多因素Logistic回归分析显示TC、TG、LDL-C及Lp(a)水平升高与黄斑HEs的发生相关。受试者工作特征(ROC)曲线分析显示,TC、TG、LDL-C、Lp(a)单项及联合检测预测NPDR患者黄斑HEs的曲线下面积(AUC)分别为0.785、0.718、0.784、0.742和0.911,联合模型的预测效能最高。

结论:血脂异常与T2DM合并NPDR患者黄斑区HEs的发生及进展密切相关。TC、TG、LDL-C及Lp(a)水平与HEs严重程度相关,提示血脂异常可能参与了黄斑HEs形成的病理过程。

关键词:2型糖尿病;非增殖期糖尿病视网膜病变;硬性渗出;血脂异常;血脂相关指标

Abstract

• AIM: To investigate the association between dyslipidemia and macular hard exudates (HEs) in non-proliferative diabetic retinopathy (NPDR) secondary to type 2 diabetes mellitus (T2DM).

• METHODS: NPDR patients attending the outpatient ophthalmology clinic from January 2021 to December 2023 were selected and divided into three groups according to the severity of macular HEs. Group A: None or minimal HEs; Group B: Definite HEs; Group C: Prominent HEs. Total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), lipoprotein(a) [Lp(a)] levels and

other lipid-related indicators were routinely measured. The correlation between these indicators and HEs was analyzed.

• RESULTS: Group A (24 eyes) consisted of 9 males and 15 females with the mean age of 54.71±6.15 y, group B (52 eyes) consisted of 20 males and 32 females with the mean age of 55.08±6.27 y, group C (14 eyes) consisted of 9 males and 5 females with the mean age of 53.93±6.08 y. The concentration of TC, TG, LDL-C and Lp(a) was highest in group C, followed by group B and lowest in group A with statistically significant differences (P<0.001). There were no statistically significant differences between the three groups for fasting plasma glucose (FPG), glycated hemoglobin A1c (HbA1c), creatinine (Cr), and HDL-C (P>0.05). The results of multivariate Logistic regression analysis showed that elevated levels of TC, TG, LDL-C, and Lp(a) were associated with the presence of macular HEs. Receiver operating characteristiccurve analysis showed that the area under the curve (AUC) for TC, TG, LDL-C, Lp(a), and their combination in predicting macular HEs in NPDR were 0.785, 0.718, 0.784, 0.742, and 0.911, respectively, with the combined model demonstrating the highest predictive performance.

• CONCLUSION: Dyslipidemia is closely associated with the development and progression of macular HEs in patients with NPDR and T2DM. The levels of TC, TG, LDL-C, and Lp(a) were correlated with the severity of macular HEs, suggesting that dyslipidemia may be involved in the pathological process of macular HEs formation.

• KEYWORDS: type 2 diabetes mellitus; non-proliferative diabetic retinopathy; hard exudates; dyslipidemia; lipid-related indicators
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INTRODUCTION

Diabetic retinopathy (DR) is a devastating disease that is one of the most common complications of diabetes and the leading cause of visual impairment and blindness in the working population[1]. With the increase in the predicted incidence of diabetes and the increased life expectancy of patients, the consequences of blindness and visual impairment due to DR have received increasing attention[2-3]. Hard exudates (HEs) are one of the most common early clinical signs of DR. HEs are lipid-rich deposits resulting from breakdown of the blood-retinal barrier and leakage of plasma lipoproteins into the retinal extracellular space[4]. They are a common and early clinical manifestation of DR and a key contributor to vision loss in patients with non-proliferative diabetic retinopathy (NPDR), particularly when they located in the central macula. Accumulating evidence suggests that subretinal fibrosis and irreversible visual impairment may follow persistent HEs, underscoring the importance of early identification and intervention[4-5].

Lipid metabolism plays an important role in the formation of HEs. Dyslipidemia, characterized by elevated levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and lipoprotein(a) [Lp(a)], as well as reduced high-density lipoprotein cholesterol (HDL-C), is increasingly recognized as a modifiable risk factor implicated in the progression of DR[6]. Dyslipidemia may promote retinal inflammation and oxidative stress, leading to increased microvascular permeability and endothelial dysfunction, which in turn facilitate the extravasation of lipids into the macula[7-8]. Moreover, specific lipid-related markers such as non-HDL-C and the triglyceride-glucose (TyG) index have emerged as sensitive indicators of metabolic dysregulation associated with microvascular complications[9]. Despite these mechanistic insights, studies on the relationship between HEs and lipid abnormalities in patients with type 2 diabetes mellitus (T2DM) are limited, and it remains controversial whether dyslipidemia can affect HEs[10]. This study aims to demonstrate the relationship between HEs and lipid-related indicators in patients with NPDR and to provide new strategies for prevention, early diagnosis and treatment of HEs in the macular area in clinical practice. Ultimately, this will improve the visual prognosis and quality of life of diabetic patients.

PARTICIPANTS AND METHODS

Ethical Approval Approval was obtained from the Ethics Committee of the Second People's Hospital of Lianyungang (Approval No.2024K113). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. All participants signed an informed consent form before enrolment.

Participants We enrolled ninety patients (90 eyes) with NPDR who attended our outpatient ophthalmology clinic from January 2021 to December 2023 and divided them into three groups. Among them, there were 38 males and 52 females, aged between 40 and 70 y, with a mean age of 54.8±6.21 y. The inclusion criteria were as follows: 1) patients with T2DM; 2) severe NPDR in at least one eye, as defined by the 2022 Chinese Guidelines for the Clinical Diagnosis and Treatment of Diabetic Retinopathy[11]; 3) no other systemic diseases; 4) patients with other retinal diseases, such as retinal vein occlusion, macular hole, macular pucker, age-related macular degeneration or hereditary retinal diseases, were excluded; 5) no other significant eye diseases; 6) no treatment for related fundus lesions.

The exclusion criteria were as follows: 1) the presence of other types of diabetes; 2) the presence of a malignant tumour; 3) severe dysfunction of any major organs; 4) a history of intraocular surgery; 5) uncontrolled hypertension; 6) autoimmune diseases; 7) opacity of the ocular media; 8) pregnancy or lactation; 9) dyslipidemia managed with medication.

Fundus Examination and Assessment All participants

underwent a comprehensive fundus examination including visual acuity testing, fundus color photography, fundus fluorescein angiography (FFA) and optical coherence tomography (OCT). OCT and fundus color photography were used to assess the severity of HEs in the macular area. Subjects were grouped according to the severity of HEs in the macular area, and eyes with severe exudation were included in the study[4,10].

Fundus Photography Grading According to the modified Airlie House classification[12], a stereoscopic fundus photograph centered on the macula was obtained using the Zeiss Visucam fundus camera. Three experienced observers graded the HEs in the photographs using the modified Airlie House classification system. Standard 45-degree stereoscopic fundus photographs from fields 2-7 were used. HEs in the macular area: HEs are small, white or yellowish-white deposits with sharp edges. They often have a slightly waxy or glistening appearance. In this study, HEs within a radius of 3 mm centered on the macular fovea was observed and the enrolled subjects were divided into three groups according to the severity of the HEs.

Group A: None or minimal HEs (Figure 1A). Level 0: absence of HEs. Level 1: questionable quantity of HEs. Level 2: definite HEs covering an area smaller than the standard image size of 3[12]. Subjects in this group showed no obvious HEs in the macular area on fundus examination. Patients' vision was average or slightly reduced, and there were few retinal microaneurysms and minimal or no HEs.

Group B: Definite HEs (Figure 1B). Level 3 corresponds to HEs that are equal to or greater than standard image 3, but less than standard image 5. Level 4 indicates HEs that are greater than standard image 5, but less than standard image 4[12]; On fundus examination, subjects showed a small amount of macular HEs involving an area of less than 1/2 papillary diameter. Visual acuity decreased slightly to moderately, the number of retinal microaneurysms increased and there were a certain number of hemorrhagic spots. The structure of the macular area did not change significantly.

Group C: Apparent HEs (Figure 1C). Level 5: Level 5 represents HEs equal to or exceeding standard image 4[12]. Fundus examinations of this group showed obvious hemorrhagic exudates in the macular area, with an area greater than or equal to 1/2 of the posterior pole. The patients' visual acuity was significantly reduced and there was an increase in the number of retinal microaneurysms and hemorrhagic spots. The HEs were abundant and the macular area's structure was significantly damaged, which may be associated with macular edema.

Demographic Characteristics and Biochemical Indexes General patient information was collected, including gender and age, duration of diabetes, history of hypertension, detailed treatment protocol for T2DM, and lifestyle factors at the first visit. In addition, 4 mL of venous blood was collected from each participant. Fasting plasma glucose (FPG), glycated hemoglobin A1c (HbA1c), creatinine (Cr), TC, TG, LDL-C, HDL-C and Lp(a) levels were routinely measured and analyzed.

Statistical Analysis SPSS software (SPSS, Inc. 25.0, Chicago, IL, USA) was used for statistical analysis. Baseline parameters, including participant gender and age, duration of diabetes, history of hypertension, and treatment protocol for T2DM, were described as mean±standard deviation or median (interquartile range). G * Power software (G * Power 3.1.9.7) was used for power analysis. According to the data distribution, comparisons between groups were analyzed by one-way analysis of variance (ANOVA) or Chi-squared test. A univariate analysis was performed, using blood lipid-related biochemical indicators as the independent variables and the presence or absence of HEs in the macular area as the dependent variable. Multivariate logistic regression analysis was used to evaluate the association between macular HEs and lipid-related indicators. Receiver operating characteristic (ROC) was used to assess the predictive value of blood lipid-related indicators for macular HEs in NPDR. $P<0.05$ was

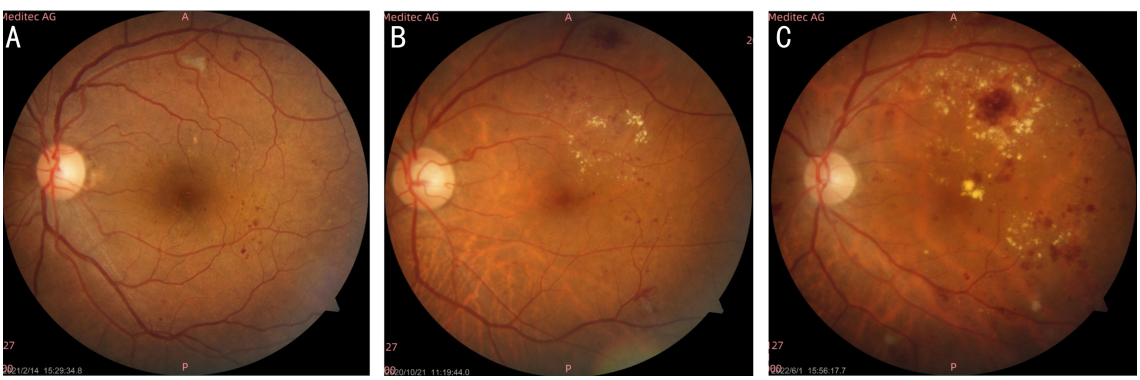

Figure 1 Three representative fundus photographs in each group A: None or minimal HEs (HEs are present above the fovea of the macula, meeting the criteria for the mildest form of HEs); B: Definite HE (HEs are located superotemporally to the fovea of the macula and demonstrate an area approximately four to five times greater than that in A, affecting less than half the macular area); C: Prominent HEs (extensive HEs with dot and blot hemorrhages are present temporal to the fovea of the macula). This presentation fulfils the most severe criteria for HE classification, involving ≥1/2 of the macular area. HEs: Hard exudates.

considered statistically significant.

RESULTS

Baseline Demographic and Clinical Characteristics In this study, 90 patients were selected and divided into three groups according to the presence and amount of HEs: group A (24 eyes) with no obvious HEs; group B (52 eyes) with a small amount of HEs; and group C (14 eyes) with obvious HEs. There were no significant differences in baseline clinical characteristics, such as gender and age distribution, duration of T2DM, prevalence of hypertension and treatment protocol for T2DM, among the three groups (P>0.05, Table 1).

Comparison of the Blood Lipid-related Biochemical Indicators Concentrations of TC, TG, LDL-C, and Lp(a) were highest in group C, followed by group B and lowest in group A. These differences were statistically significant (P<0.001). No statistically significant differences were observed between these groups for FPG, HbA1c, Cr, and HDL-C (Table 2). A post-hoc power analysis (G * Power 3.1.9.7) based on TC, TG, LDL-C, Lp(a) (P<0.001) showed a large effect size (effect size f=0.422, 0.650, 0.598, 0.684, respectively), with a power of 95% using G * Power software. The sample size is sufficient to demonstrate the robustness of the analytical effects.

Further comparative analysis among these groups revealed varying degrees of statistical differences in TC, TG, LDL-C, and Lp(a) levels among different groups (Figure 2).

Table 1 Demographic characteristics of the enrolled subjects

Groups	Eyes (n)	Gender (M/F)	Age ($\bar{x}\pm s$, y)	Duration of T2DM ($\bar{x}\pm s$, y)	Hypertension (n)	Treatment protocol for T2DM(n)		
						Insulin	Oral hypoglycemic drugs	Untreated
Group A	24	9/15	54.71 ±6.15	7.95 ±1.46	13	14	8	2
Group B	52	20/32	55.08 ±6.27	7.61 ±1.34	36	34	15	3
Group C	14	9/5	53.93 ±6.08	8.09 ±2.03	10	11	2	1
F/χ^2		3.315	1.835	3.176	1.904		1.926	
P		0.191	0.542	0.294	0.386		0.729	

For categorical variables such as gender, history of hypertension, and T2DM treatment protocol, the Chi-square test demonstrates significant differences between groups. For continuous variables such as age and duration of T2DM, analysis of variance was used for the same purpose. T2DM: Type 2 diabetes mellitus.

Table 2 Comparison of the blood lipid-related biochemical indicators in three groups

Lipid-related indicators	Group A	Group B	Group C	F	P
Eyes (n)	24	52	14	-	-
FPG ($\bar{x}\pm s$, mmol/L)	8.06±2.08	7.83 ±1.22	7.59 ±1.35	2.265	0.455
HbA1c ($\bar{x}\pm s$, mmol/L)	7.42±1.63	7.86±1.25	8.19 ±1.44	4.396	0.152
Cr ($\bar{x}\pm s$, mmol/L)	89.11 ±14.59	91.96±16.32	93.34±17.60	2.379	0.430
TC ($\bar{x}\pm s$, mmol/L)	4.95 ±1.13	5.74 ±1.21	6.62 ±1.48	11.754	<0.001[a]
TG ($\bar{x}\pm s$, mmol/L)	1.71 ±0.35	2.16±0.48	2.59±0.51	18.918	<0.001[a]
LDL-C ($\bar{x}\pm s$, mmol/L)	2.97±0.54	3.62±0.68	4.08 ±0.77	15.648	<0.001[a]
HDL-C ($\bar{x}\pm s$, mmol/L)	1.28±0.29	1.19 ±0.24	1.13 ±0.21	5.070	0.100
Lp(a) ($\bar{x}\pm s$, mg/L)	411.16 ±41.79	472.38 ±52.15	515.67 ±58.42	19.239	<0.001[a]

[a]Statistically significant. FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin A1c; Cr: Creatinine; TC: Total cholesterol; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; Lp(a): Lipoprotein(a).

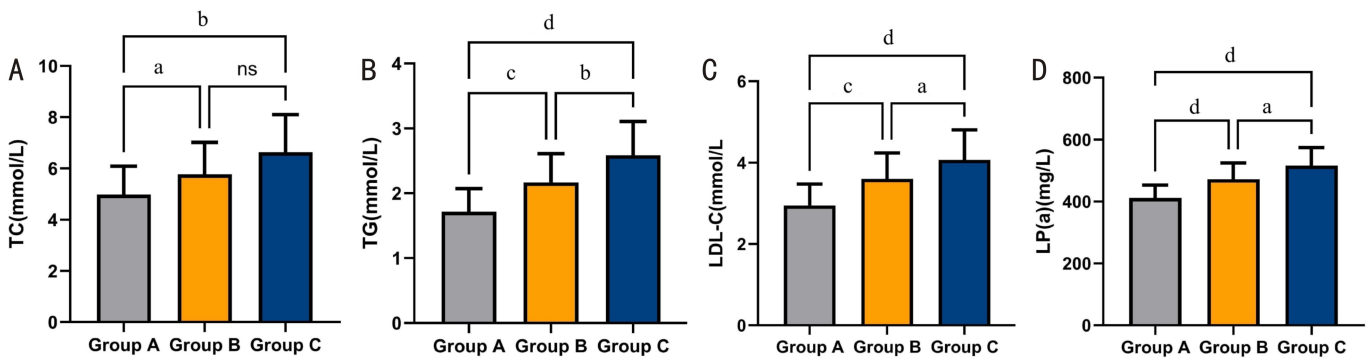

Figure 2 Comparison of serum expression levels of TC, TG, LDL-C, and Lp(a) in three groups A: The statistical graph of TC expression in three groups; B: The statistical graph of TG expression in three groups; C: The statistical graph of LDL-C expression in three groups; D: The statistical graph of Lp(a) expression in three groups. [a]P<0.05, [b]P<0.01, [c]P<0.001, [d]P<0.0001. ns: Not significant; TC: Total cholesterol; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein(a).

Univariate Analysis A univariate analysis was performed with blood lipid-related biochemical indicators as the independent variables and the presence or absence of HEs in the macular area as the dependent variable. Variables with $P<0.05$ threshold in the univariate analysis were incorporated into the multivariate logistic regression analysis (Table 3). Therefore, TC ($P=0.002$), TG ($P<0.001$), LDL-C ($P<0.001$) and Lp(a) ($P<0.001$) were included in the model.

Multivariate Logistic Regression Analysis Multivariate logistic regression analysis was performed to further evaluate the associations between blood lipid-related biochemical indicators and macular HEs. Based on a comprehensive evaluation of univariate analysis results and clinical relevance, we selected the following variables for multivariable logistic regression analysis. When TC, TG, LDL-C and Lp(a) were used as independent variables, TC ($OR=1.677$, 95% CI: 1.113-2.526, $P=0.014$), TG ($OR=1.522$, 95% CI: 1.117-2.074, $P=0.008$), LDL-C ($OR=1.857$, 95% CI: 1.176-2.932, $P=0.008$) and Lp(a) ($OR=1.490$, 95% CI: 1.060-2.096, $P=0.022$) contributed to the occurrence and severity of HEs (Table 4).

Predictive Value of Blood Lipid-related Biochemical Indicators of Macular HEs The ROC curve was used to evaluate the ability of TC, TG, LDL-C, Lp(a) and their combination to predict NPDR with macular HEs. The areas under the curves for the individual predictors and the combined predictor were found to be 0.785, 0.718, 0.784, 0.742, and 0.911, respectively (Figure 3, Table 5).

Table 3 Associations between blood lipid-related biochemical indicators and macular HEs by univariate analysis

Factors	No HEs in the macular area ($n=24$)	HEs in the macular area ($n=66$)	F/t	P
Age ($\bar{x}\pm s$, y)	54.83±6.02	54.82±6.31	0.010	0.992
Duration of T2DM ($\bar{x}\pm s$, y)	7.96±1.55	7.70±1.56	0.705	0.483
Gender, n (%)			0.299	0.584
Male	9 (37.5)	29 (43.9)		
Female	15 (62.5)	37 (56.1)		
Hypertension, n (%)			1.880	0.170
Present	11 (45.8)	20 (30.3)		
Absent	13 (54.2)	46 (69.7)		
Treatment protocol for T2DM, n (%)			0.760	0.684
Insulin	14 (58.3)	45 (68.2)		
Oralhypoglycemicdrugs	8 (33.3)	17 (25.8)		
Untreated, n (%)	2 (8.3)	4 (6.1)		
FPG($\bar{x}\pm s$, mmol/L)	8.03±2.04	7.77±1.22	7.252	0.559
HbA1c ($\bar{x}\pm s$, mmol/L)	7.42±1.68	7.95±1.25	4.933	0.169
Cr ($\bar{x}\pm s$, mmol/L)	89.11±14.56	92.25±16.50	1.257	0.413
TC ($\bar{x}\pm s$, mmol/L)	4.97±1.11	5.95±1.34	0.838	0.002
TG ($\bar{x}\pm s$, mmol/L)	1.72±0.36	2.26±0.49	2.979	<0.001
LDL-C ($\bar{x}\pm s$, mmol/L)	2.95±0.53	3.70±0.68	3.375	<0.001
HDL-C ($\bar{x}\pm s$, mmol/L)	1.26±0.31	1.17±0.21	6.056	0.215
Lp(a) ($\bar{x}\pm s$, mg/L)	411.16±41.77	481.58±51.99	1.909	<0.001

HEs: Hard exudates; T2DM: Type 2 diabetes mellitus; FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin A1c; Cr: Creatinine; TC: Total cholesterol; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; Lp(a): Lipoprotein(a).

Table 4 Associations between blood lipid-related biochemical indicators and macular HEs by multivariate logistic regression analysis

Factors	β	SE	Wald	P	OR	95%CI
TC	0.517	0.209	6.119	0.014[a]	1.677	1.113-2.526
TG	0.420	0.158	7.066	0.008[b]	1.522	1.117-2.074
LDL-C	0.619	0.233	7.058	0.008[b]	1.857	1.176-2.932
Lp(a)	0.399	0.174	5.258	0.022[a]	1.490	1.060-2.096
HDL-C	0.211	1.819	0.014	0.907	1.235	0.035-3.691
HbA1c	0.300	0.319	0.884	0.347	1.350	0.722-2.521
Hypertension	1.269	0.920	1.985	0.159	0.274	0.045-1.660
Duration of T2DM	0.046	0.292	0.025	0.874	1.048	0.591-1.858

[a]$P<0.05$, [b]$P<0.01$. HEs: Hard exudates; TC: Total cholesterol; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein (a); HDL-C: High-density lipoprotein cholesterol; HbA1c: Glycated hemoglobin A1c. SE: Standard error; OR: Odds ratio.

Table 5 The predictive value of TC, TG, LDL-C, Lp(a) and their combination for macular HEs

Indicator	Optimal cut-off value	AUC	*P*	95%*CI*	Sensitivity(%)	Specificity(%)
TC(mmol/L)	4.86	0.785	<0.001	0.676-0.871	80.77	66.67
TG(mmol/L)	1.76	0.718	<0.001	0.603-0.815	82.69	62.50
LDL-C(mmol/L)	3.30	0.784	<0.001	0.675-0.870	59.62	91.67
Lp(a)(mg/L)	435.69	0.742	<0.001	0.628-0.835	69.23	70.83
Combination of the four	-	0.911	<0.001	0.823-0.964	76.92	91.67

HEs: Hard exudates; TC: Total cholesterol; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein (a); AUC: Area under the curve.

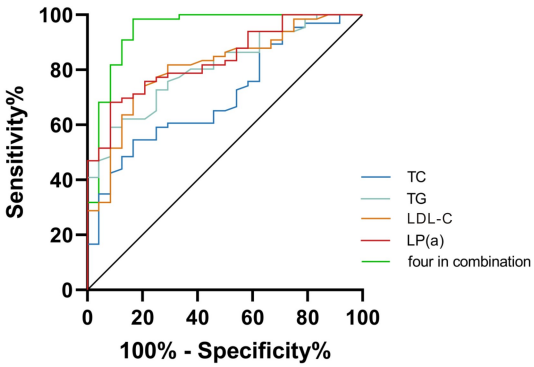

Figure 3 Receiver operating characteristic curve analysis to predict the factors affecting macular HEs TC: Total cholesterol; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein(a).

DISCUSSION

DR is the most common complication of diabetes mellitus and the leading cause of preventable blindness in the working population[13]. HEs in the macula are a major factor leading to poor prognosis of diabetic macular edema (DME) and visual impairment in patients with NPDR[14]. Long-term accumulation of HEs can lead to tissue fibrosis, with subretinal fibrosis having a severe and irreversible impact on patients' vision[15-16]. Therefore, effective prevention and early detection of HEs in the macula of patients with NPDR is crucial to prevent blindness and mitigate visual impairment.

Dyslipidemia is common in patients with T2DM. Previousstudies have shown that dyslipidemia not only poses a significant risk for cardiovascular disease, but also makes diabetic patients more susceptible to DR[17-19]. Zhang *et al*[20] indicated that dyslipidemia is associated with the incidence and progression of macular edema in patients with T2DM. In this study, ninety patients with NPDR due to T2DM were selected and divided into three groups according to the severity of HEs in the macular area. The primary data such as gender, age, medical history, blood routine, and blood lipid related indicators of each group were compared. The results showed a clear correlation: the higher the concentration of serum TC, TG, LDL-C, and Lp(a), the more severe HEs in the macular area. Notably, there was no significant difference in other indicators between the groups, suggesting that TC, TG, LDL-C, and Lp(a) are closely related to the onset and progression of macular HEs. The etiology of NPDR is complex and its pathogenesis involves multiple factors, including inflammatory response, oxidative stress, vascular leakage or angiogenesis, and cathepsin[21-22]. TC is an essential component of the cell membrane. However, high levels of TC can lead to endothelial cell injury, vascular inflammation, oxidative stress, and endothelial dysfunction, resulting in retinal microvascular damage and accelerating the onset and progression of NPDR[16,23].

TG, which primarily serves as an energy reserve in adipose tissue, shows a positive correlation with macular retinal thickness when maintained at high levels over time. This macular retinal thickening can severely affect a patient's vision[17,24]; at the same time, high levels of TG can cause insulin resistance, inflammatory response, and oxidative stress, which in turn affect retinal vascular function and increase the risk of progression to PDR[25-26]. LDL-C is the main carrier of cholesterol. High levels of LDL-C not only render the vascular wall susceptible to oxidative damage and inflammatory responses[27], but also induce changes in retinal intimal permeability by upregulating adhesion molecule expression, activating platelets, and promoting vascular endothelial cell aggregation in the macular region. These changes result in HEs forming in the macular area. Patients with elevated serum LDL-C levels are more likely to have retinal HEs[28]. Lp(a) is a blood lipoprotein synthesized by the liver. Elevation of Lp(a) can induce oxidative stress and inflammatory response by interacting with the retinal vascular wall, further damaging vascular endothelial cells and increasing retinal exudation[29]. The levels of TC, TG, LDL-C, and Lp(a) were correlated with the severity of macular HEs, suggesting that dyslipidemia may be involved in the pathological process of macular HE formation[24]. This could be attributed to the fact that elevated levels of TC and LDL-C may disrupt lipid metabolism, increase the lipid content of exudates, and consequently aggravate microvascular damage and leakage in the macular region[30].

The damage to visual function caused by HEs in the macula is irreversible. Once it occurs, it can only be managed by slowing the progression of the disease. Therefore, it is crucial to identify suitable predictive indicators to prevent the

occurrence of HEs in the macular area. In our study, the results of multivariate logistic regression analysis showed that elevated levels of TC, TG, LDL-C, and Lp(a) were independently associated with the presence of macular HEs, suggesting that lowering these lipid levels may help to minimize the occurrence of HEs. Furthermore, ROC curve analysis showed that TC, TG, LDL-C, and Lp(a) each had specific predictive values for NPDR macular HEs, with the combined predictive value having the highest value. This provides us with new strategies for the prevention, diagnosis and treatment of macular HEs in clinical practice, and more attention should be paid to monitoring blood lipids in diabetic patients and actively managing blood lipid levels to prevent and mitigate the onset and progression of macular HEs.

Several limitations of this study should be acknowledged. First, this is a cross-sectional study that reveals the correlation between dyslipidemia and macular HEs, yet it does not establish whether dyslipidemia directly causes macular HEs. Second, excluding patients receiving lipid-lowering therapy effectively reduced treatment-related confounding; however, it limits the generalizability of our findings to real-world diabetic populations. This exclusion criteria may result in a study sample that is not fully representative of current clinical practice, and therefore, our findings should not be directly extrapolated to patients on lipid-lowering medications. As highlighted in previous studies[31-34], future research should examine whether lipid-lowering therapy modifies the associations observed in untreated diabetic patients and whether specific drug classes (*e.g.*, statins, fibrates, PCSK9 inhibitors) differentially influence the development of macular HEs. Third, no statistically significant differences were observed between groups in these variables—blood pressure levels, duration of diabetes, LDL-C levels, and renal function—in either univariate or multivariable logistic regression analyses. These null findings may be attributed to potential selection bias and limited statistical power. Given the small sample size in group C, the ability to detect modest or weak associations may have been reduced. However, the small sample size in group C, resulting from practical challenges such as patient adherence and completeness of follow-up, may limit the statistical power of subgroup comparisons. Although post-hoc power analysis using G*Power indicated a power of 95%, the risk of type II error still exists, and the generalizability of the findings should be interpreted cautiously. Further studies with longer follow-up and larger sample sizes, or glycemic control, blood pressure and renal function, may be necessary to evaluate long-term effects. Besides, the assessment of HEs using fundus photography remains subjective. Future studies should integrate multimodal imaging with automated segmentation algorithms and artificial intelligence-based image analysis to enhance statistical power and establish a more robust and evidence-based grading system. In addition, in this study only included traditional blood lipid indicators such as TC, TG, LDL-C, and Lp(a) were involved. Future studies may contemplate the incorporation of novel indicators to further reveal the complex relationship between dyslipidemia and DR. Finally, even at the same level of dyslipidemia, the severity of macular HEs the patient's eyes exhibits asymmetry, suggesting that HEs are also influenced by the combined effects of systemic factors and local microvascular lesions, which requires further investigation. This intriguing interplay warrants further investigation. In conclusion, dyslipidemia is strongly associated with the development and progression of macular HEs in patients with type 2 NPDR. The levels of TC, TG, LDL-C, and Lp(a) were correlated with the severity of macular HEs, suggesting that dyslipidemia may be involved in the pathological process of macular HE formation. Therefore, it is crucial to priorities the monitoring and regulation of blood lipids in the clinical management and treatment of diabetic patients. This approach is essential to prevent and treat macular HEs, improve visual function and reduce the risk of blindness. Future research should focus on the relationship between dyslipidemia and macular HEs to identify more precise prevention and treatment strategies. These efforts will undoubtedly provide invaluable practical guidance for clinical practice.

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