Review Article

Lipoprotein (a) as a predictor of diabetic retinopathy in patients with type 2 diabetes: A systematic review

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Abstract

Background: Lipoprotein a (LP(a)), an LDL-like lipoprotein, known as a risk factor for cardiovascular diseases, has a controversial association with diabetic retinopathy in patients with type 2 diabetes—the current systematic review aimed to critically assess the association between LP(a) and diabetic retinopathy.

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Methods: A systematic review of relevant studies was conducted after a thorough search in PubMed, Scopus, and Google Scholar electronic databases. We used English observational, case-control, and prospective cohort studies published up to August 2022, including type 2 diabetic patients as the population, diabetic retinopathy as the outcome, and LP(a) as the intervention.

Result: 17 relevant studies, including 4688 patients with diabetes, were included in this systematic review. While in 13 studies, Lipoprotein(a) was recognized as a risk factor for diabetic retinopathy, only three studies reported no evidence of a relationship between the two. Also, another study showed a mixed outcome of the relationship between LP(a) and diabetic retinopathy.

Conclusion: High serum lipoprotein(a) in patients with type 2 diabetes is considered a risk factor for diabetic retinopathy. However, further large-scaled cohort studies are still required to validate this finding.

Keywords

Lipoprotein (a), type 2 diabetes mellitus, diabetic retinopathy, systematic review

Introduction

Diabetes as a chronic disease with an increasing prevalence globally has gained the attention of many medical researchers. According to WHO (World Health Organization), The number of patients with diabetes has raised from 108 million in 1980 to 422 million in 2014.[1] Fundamental factors that make an individual susceptible to the disease vary from environment to genetics. Patients with diabetes are at risk for multiple complications such as retinopathy, nephropathy, and cardiovascular events.

Diabetic retinopathy is a serious microvascular complication of diabetes that is the primary cause of vision loss in adults of working age worldwide.[2] Nearly all patients with type 1 diabetes and >60% of patients with type 2 diabetes (T2DM) have diabetic retinopathy (DR);[3] for example, in Iran, 37.8% of patients with T2DM have DR.[3,4] As the population affected by this condition grows, several risk factors are considered to be linked with DR. However, it should be noted that the predicting value of these factors is still the topic of many studies. Some patients with controlled blood glucose levels have shown worsening symptoms and signs of DR; on the contrary, there are patients with long-time diabetes whose DR has not occurred.[5] Therefore, the need to outline the predisposing factors remains. Several studies have proposed the relationship between lipid profile and DR.[6–9] According to these studies, lipoprotein(a) (LP(a)) and some apolipoproteins, such as apolipoprotein B (ApoB) and ApoA1 and the ApoB-to-ApoA ratio, could be reliable indicators of severity and prognosis of DR compared to routine lipid profile components such as low-density lipoprotein (LDL), high-density lipoprotein (HDL) or LDL-to-HDL cholesterol ratio.

LP(a) is an LDL-like lipoprotein containing an apolipoprotein B-100 molecule linked to a large glycoprotein called ApoA via a disulfide bond. LP(a) is considered a more prothrombotic and atherogenic molecule than LDL[10] and is increased in patients with diabetes, especially those with poor glycemic control and long-duration disease. Most studies before the 2000s considered LP (a) as an independent factor for DR with an unknown mechanism.[7–9] However, this statement is now a topic of debate as studies are divided into two groups of confirming[11] and opposing[12] the former findings based on a mechanism approach.

During disease progression, inflammatory molecules are produced, and angiogenesis occurs. Furthermore, VEGF is overexpressed by the maintained hyperglycemic environment and up-regulated by tissue hypoxia. Also, pro-inflammatory mediators regulated by cytokines, such as tumor necrosis factor (TNF-α) and interleukin-1 beta (IL-1β), and growth factors lead to the progression of these processes, culminating in vasopermeability (diabetes macular edema) and/or pathological angiogenesis (proliferative diabetic retinopathy).

According to this controversy that obscured the relationship between LP(a), local inflammation, and diabetic retinopathy, this systematic review study aims to critically discuss the role of LP (a) as a predictive factor for DR.

Methods

Search strategy

This study conformed to the favored Reporting Items for Meta-Analyses and Systematic Reviews (PRISMA) statement and a meta-analysis of monitoring studies in epidemiology (MOOSE) guidelines. PubMed, Google Scholar and Scopus were searched to identify all accessible, relevant studies up to August 2022. We applied the following MeSH terms for search: "'Diabetic Retinopathy,' 'Diabetes complications,' 'Diabetes Mellitus, Type 2', 'Lipoprotein(a).'" Critical words utilized in the search included "Risk factor," "Lipoprotein A," and "diabetic retinopathy." No language or other limitations were

adjusted in this research. The protocol of this systematic review has been registered on The Open Science Framework (OSF) (available at https://osf.io/fcxsy/)

Study selection

The authors separately screened the studies by the title and abstract to eliminate those unrelated to the research point of interest. The full text of selected studies was examined to discover the inclusion of the related data.

In this systematic review, an accurate search was performed through the available published cross-sectional studies, case-control studies, and prospective cohort studies to justify the possible association between Lp(a) and the incidence of DR in patients with T2DM.

Data extraction

For each selected study, the following variables were extracted: the first author's last name, geographic location(s), year of publication, number of all the participated subjects and cases, data source, study type, duration of follow-up in cohort studies, confounders for adjustment, and effect size estimates with conforming 95% confidence intervals (Cis) of all the registered papers. Studies in which more than one calculation of effect was reported, we selected the 'most adjusted' estimate in this research.

Methodological quality assessment

All selected studies were assessed according to the JBI Critical Appraisal tools (https://jbi.global/critical-appraisal-tools) depending on the study design, using The JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies (11 articles), The JBI Critical Appraisal Checklist for Case-Control Studies (2 articles), and The JBI Critical Appraisal Checklist for Cohort Studies (4 articles).

Results

Literature search

Figure 1 presents the Prisma flow diagram of the current study. Briefly, 5116 studies were retrieved via primary literature search in PubMed, Scopus, and Google Scholar databases after excluding the duplications. Among which, 5066 that did not apply to the research purpose had been excluded after screening the title/abstract of the articles. Subsequently, 50 potential applicable records went through full-text review. Of these, 31 were also eliminated. Finally, 17 observational studies, including four prospective cohort research,[7,11,13,14] eleven cross-sectional studies,[8,9,15–23] and two nested case-control studies,[24,25] were included in the systematic review.

Study characteristics and quality evaluation

The characteristics of the selected articles have been summarized in Table 1. 17 articles with 4688 patients with T2DM were covered. The studies were carried out in Korea,[8,14] China,[21,23] Japan,[7,9,15] Republic of Serbia,[25] Iran,[11] the United States,[20] India,[16,24] Turkey,[17,18] Italy,[19] Egypt[22] and Belgium.[13] The mean ages of the patients varied from 45 to 70 years. The follow-up duration of the cohorts ranged from 5 to 11 years.

In 13 articles, Lp(a) was described as a risk factor for DR[7–9, 11, 14–16, 19, 21–25]; in three studies, there was no significant association between the serum Lp(a) ranges and DR in patients with T2DM[17,18,20]; while another study reported a significant association between Lp(a) and DR.[13]

Potential confounding factors adjusted in the studies included age, smoking, sex, body mass index, HbA1c, HDL cholesterol, LDL cholesterol, Levels of Lp(a), usage of antidiabetic pills, and lipid-lowering therapies. Table 2

Discussion

This systematic review of 4688 participants critically assessed the association between LP(a) and DR. It was concluded that higher Lp(a) levels is generally associated with increased risks of both the development and severity of DR.

The relationship between lipoprotein (a) and diabetic retinopathy was consistent with many of the previous studies in which Lp(a) was evaluated as a categorical or continuous variable.[7,8,11,13–17,19–25] The included studies supported the relationship between higher serum Lp (a) and diabetic retinopathy. Moreover, the link between Lp(a) and DR appeared more apparent in research from 2017 onwards than in studies before 2017.[9,16–18,20] Jenkins et al. suggested that Lp(a) could affect the potential relationship between diabetic retinopathy and atherosclerosis and proposed Lp(a) as an independent risk factor for microvascular complications of diabetes.[26] Yun et al., in a long-term prospective cohort study, found that even in DM patients with a mean $HbA_{1c} < 7.0\%$, Lp(a) level remained a significant risk factor for future DR. However, the elevated Lp (a) failed to show any effect on the pan-retinal photocoagulation (PRP) or pars plana vitrectomy (PPV). This might be because these procedures are indicated for patients with proliferative retinopathy,[14] which takes a more significant amount of time (more than 20 years) to develop compared to the timespan of this study.[27]

Despite the lack of proper evidence in early studies on the relationship between LP(a) and DR, recent studies have suggested some possible mechanisms that clarify the role of LP(a) as a predictive biomarker.[11] Lp(a) can affect oxidized lipids, vascular tone, and perfusion and can enhance oxidative stress through the production of reactive

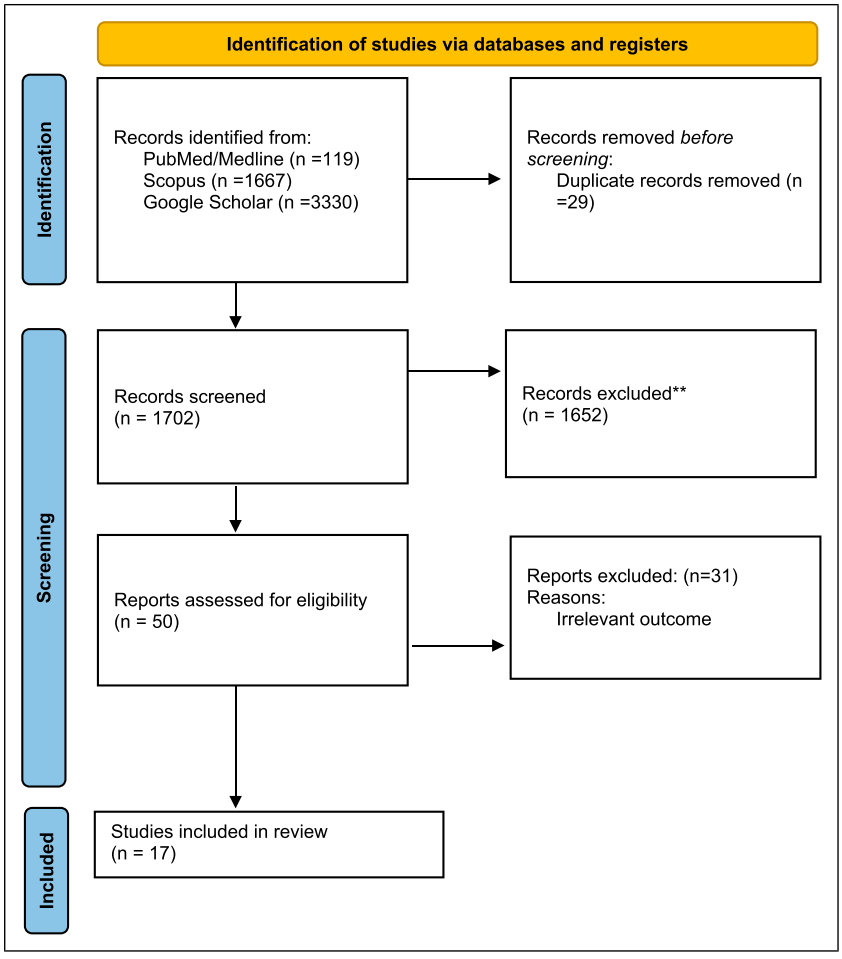

Figure 1. PRISMA flow diagram.

Table 1. The search strategy of pubmed, scopus and google scholar.

Data base	Search terms	Results (search date: August 18, 2022)
PubMed	(("Diabetic Retinopathy"[Mesh] OR ("diabetes Complications"[Mesh]) AND (("diabetes mellitus, type 2"[Mesh]) OR ("insulin Resistance"[Mesh]) OR ("glucose Intolerance"[Mesh])) AND (("Lipoprotein(a)"[Mesh]) OR ("LP(a)"[tiab]))	119
Scopus	((TITLE-ABS-KEY (diabetic AND retinopathy) OR TITLE-ABS-KEY (diabetic AND retinopathies) OR TITLE-ABS-KEY (retinopathies, AND diabetic) OR TITLE-ABS-KEY (retinopathy, AND diabetic))) AND ((TITLE-ABS-KEY (lipoprotein AND a) OR TITLE-ABS-KEY (apolipoprotein*))) AND ((TITLE-ABS-KEY (type 2 diabetes AND mellitus) OR TITLE-ABS-KEY (diabetes AND mellitus, AND noninsulin-dependent) OR TITLE-ABS-KEY (diabetes AND mellitus, AND type AND ii) OR TITLE-ABS-KEY (type 2 diabetes) OR TITLE-ABS-KEY (maturity-onset AND diabetes AND mellitus) OR TITLE-ABS-KEY (diabetes AND mellitus, AND adult-onset)))	1667
Google scholar	("Diabetic retinopathy") AND (("lp(a)" OR "LP (a)" OR "lipoprotein(a)" OR "lipoprotein (a)")	3330

Table 2. Summary of the included studies.

First author	Country	Type of study	year	Study participation	Mean age	Lp(a) presentation	Follow up duration	Definition of diabetic retinopathy	Variable adjustment	Mean outcomes	Quality score
Deepa[16]	India	Cross-sectional	2002	725 T2DM patients (male)	54 ± 10	Continuous	1 year	Retinopathy was diagnosed when there was evidence of microneurysms, dot hemorrhages, exudates or cotton wool spots in the absence of any new vessels or advanced diabetic eye disease, fibrous retinitis, vitreous, retinal detachment. NPR and PDR were taken together as retinopathy for this study	Age, male, BMI, Systolic blood pressure, Diastolic blood pressure, Fasting plasma glucose, HbA1c, serum cholesterol, Serum triglycerides, Lipoprotein, CAD, Proteinuria, PVD, Retinopathy	• Mean Lp(a) levels was higher in DR patients. (p = 0.0007)	8
Haffner[20]	U.S.A	Cross-sectional	1995	70 T2DM patients (28female & 44male)	45 ±7 & 64 ± 1	Continuous	NA	The recent appearance of new vessels or more than one of the following: Multiple hemorrhages, multiple cotton wool spots, venous irregularities, widespread capillary closure with leakage of dye on fluorescein angiography	Age, gender, duration of diabetes, glycated hemoglobin AI, systolic blood pressure, serum creatinine, proteinuria	• Lp(a) (change of 5 mg/dl) was not related to the prevalence of retinopathy (OR=0.99, 95% CI=0.88, 1.09, p = 0.840) in the overall population	7
Djericd[25]	Republic of Serbia	Case control	1998	69 IDDM & 123 control group	NA	Continuous	NA	Clinically detectable retinopathy	Levels of Lp(a)	• Lp(a) levels in the AR group (0.19 0.25 g/L) were significantly higher than in the control group of 123metabolically healthy subjects. No significant differences were found between the patients with AR and NR group (0.10 0.20 g/L). The frequency of the elevated levels of Lp(a) (over 0.25 g/L) was threefold higher in the AR (33%) than in the control group (11%)	8
Hideharu funatsu[15]	Japan	Cross sectional	2009	126 diabetic type2 patients	57±11	Continuous	2 years	Fundus findings were confirmed by standardized fundus color photography, which was performed with a topcon TRC501A fundus camera. The severity of diabetic retinopathy was graded according to the modified early treatment diabetic retinopathy study retinopathy severity scale. Evaluation was performed by 3 ophthalmologists	Age, gender, body mass index, duration of T2DM, smoking, total cholesterol-C, triglycerides, BUN, uric acids, HDL cholesterol (mmol/1), AER (pg/min)-lipoprotein (a) (mg/dl), HbA1C, blood pressure, fibrinogen	• The progression of non-proliferative diabetic retinopathy to be associated with serum levels of lp(a).(odds ratio- 2.70 [1] 95%CI) (pvalue:0.018) Lp(a) and another variable were chosen as independent variables. (odd ratio- 95% CI: 1.90) (p value:0.038)	8

(continued)

Table 2. (continued)

First author	Country	Type of study	year	Study participation	Mean age	Lp(a) presentation	Follow up duration	Definition of diabetic retinopathy	Variable adjustment	Mean outcomes	Quality score
Andina Hu[21]	China	Cross sectional	2011	25 T2DM patients (16 females - 9 males)	64±8	Continuous	NA	After mydriasis with tropicamide eye drops, a color photograph was taken of the fundus by the topcon TRC-50IA fundus camera (Topcon, Tokyo, Japan). Diabetic retinopathy was graded by two ophthalmologists based on ETDRS grading system	Sex, age, hypertension, smoking, alcohol, body mass index, HDL cholesterol, LDL cholesterol, statin, triglyceride, apolipoprotein A1, apolipoprotein B, apolipoprotein E	• NPDR and PDR progression was considerably associated with the level of Lp(a) (1.38±0.22 vs 1.22±0.26; p = 0.0290). Multivariate logistic regression analysis revealed that Lp(a) level (OR=0.026, 95%CI <0.001–0.450, p = 0.0304) for NPDR.	8
Michel P. HERMANS[13]	Belgium	Cohort	2017	280 T2DM females	68±12	Continuous	NA	Retinopathy was diagnosed by visual examination and/or fluorescein angiography	Sex, age, diabetes duration, hypertension, smoking, body circumference, family history (DM - EOCHD), HDL cholesterol, LDL cholesterol, use of insulin, statin, and, mean HbA1c, triglyceride, lipoprotein(a)	• Associated with lower prevalence of microvascular/ macrovascular complications: All-cause microangiopathy 47% vs 61%; retinopathy 22% vs 34%; all-cause macroangiopathy 19% vs 31%; and coronary artery disease 6% vs 24% (p < 0.05) and this ratio about [HDL-c/ apoa-i] is a versatile and readily available marker of cardiometabolic status and vascular complications in T2DM women	-
E.DOGAN[17]	Turkey	Cross sectional	2010	71 T2DM patients (22male, 49 female)	56 (40–70)	Continuous	NA	Ophthalmologists evaluated presence of retinopathy by eye-ground examination	Age, BMI, duration of diabetes, blood pressure, fasting serum glucose, total cholesterol, HDL, creatinine, blood urea	• Retinopathy was observed in 26% of the diabetic patients. In these patients there were no statistically significant difference between Lp(a) levels, rates or means of other variables. (p > 0.05)	7
Fatemeh moosaie[11]	Iran	Cohort	2020	1057 patients with T2DM, 637 patients without diabetic retinopathy and 420 patients with DR	-	-	5 years	Diabetic retinopathy is a critical microvascular complication of diabetes that accounts for most cases of new-onset blindness in the working-age population of developed countries	Sex, age, systolic blood pressure, HbA1c, smoking status, BMI, use of anti-dyslipidemia drug, eGFR, triglycerides, LDL, HDL, and non-HDL cholesterol	• Positive relationship between lipoprotein(a) and DR as well as a negative correlation between ApoA and DR (p < 0.001 and p = 0.03, respectively)	-

(continued)

Table 2. (continued)

First author	Country	Type of study	year	Study participation	Mean age	Lp(a) presentation	Follow up duration	Definition of diabetic retinopathy	Variable adjustment	Mean outcomes	Quality score
Morisaki[9]	Japan	Cross-sectional	1994	104 noninsulin-dependent diabetic patients (35 males, 69 females)	23 were less than 60 years of age (middle-aged), and 81 were 60 years or older	-	NA	Retinopathy is a serious complication specific for diabetes mellitus (DM),analysis showed that only HbAlc and Lp(a) (between their parameters) were independent risk factors for retinopathy in all cases and in the elderly	Levels of lipoprotein(a) (Lp(a)) and lipids, HbA1c, Other indicators possibly related to retinopathy	• Lp(a) is an independent risk factor for diabetic retinopathy	-
U G O Ergün[18]	Turkey	Cross sectional	2004	100 T2DM patients (67 females, 33males)	There were 3 groups, .56±2.9.57±3.2, .60±2.7	Continuous, Between 0 and 29.9 mg/dl, Of Lp(a) were, Accepted as normal	NA	Fundoscopic examination was performed by a senior ophthalmologist, using ophthalmoscope and/or biomicroscope through dilated pupils. The findings were graded as normal retina, nonproliferative diabetic retinopathy, and proliferative retinopathy	Age, gender, BMI, fasting plasma glucose, HbA1c, systolic blood pressure, diastolic blood pressure, serum triglyceride, blood urea nitrogen, creatinine and albumin excerion rate	• The Lp(a)Levels were similar in patients with retinopathy and those without retinopathy	8
Rupali chopra[24]	India	Case control	2007	200 T2DM patients (117 female and 83 male), 100 patients with no retinopathy served as the control group and 100 with retinopathy served as the study group	Control: 55.1, Non proliferative diabetic retinopathy: 55 proliferative diabetic retinopathy: 54	Continuous	NA	Fundus findings were graded as: 1. No signs of retinopathy 2. Nonproliferative diabetic retinopathy (NPDR) 3. Proliferative diabetic retinopathy (PDR). Individuals were classified as having PDR if they had new vessels, vitreous hemorrhage, vitreoretinal traction or retinal detachment believed to be attributable to diabetic neovascularization	Age, fasting glucose levels, triglycerides, total cholesterol, high density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol concentrations	• The average lipoprotein (a) levels in the study group (68.5 mg/dl) were significantly higher than in the control group (25.1 mg/dl) ($p < 0.001$). The lipoprotein(a) levels were found to increase with increasing severity of diabetic retinopathy	8
T onuma[7]	JAPAN	Cohort	1994	158 T2DM patients (83male-75female)	58±11	Continuous	-	Diabetic retinopathy was diagnosed using ophthalmoscopy with fluorescence angiography by ophthalmologists.	Lp(a) concentration, sex, age, BMI, duration of diabetes, ischemic heart disease, (IHD), (FPG), glycosylated hemoglobin A1c (HbAlc), total cholesterol (TO), triglyceride (TG), high-density lipoprotein cholesterol, (HDL-C)	• Mean Lp(a) levels was higher in DR patients. ($p = 0.05$)	8

(continued)

Table 2. (continued)

First author	Country	Type of study	year	Study participation	Mean age	Lp(a) presentation	Follow up duration	Definition of diabetic retinopathy	Variable adjustment	Mean outcomes	Quality score
Chul-Hee Kim[8]	Korea	Cross sectional	1998	412 outpatients with T2DM	-	Continuous	-	Diabetic retinopathy was determined by an ophthalmologist using fundoscopic examination. Fundoscopic examination was performed by a retinal specialist (Y.-H.Y.) using ophthalmoscope and/or biomicroscope through dilated pupils	Age (years)-Diabetes duration (years)-BMI (kg/m2)-Fasting serum glucose (mmol/1)-HbA! (%)-C-peptide (nmol/1). Blood pressure (mmHg), Systolic-diastolic Cholesterol (mmol/1), Triglycerides (mmol/1), HDL cholesterol (mmol/1), AER (pg/min)-Lp(a) (mg/dl)	• Subjects with PDR had higher serum lipoprotein (a) levels (32.2 ± 3.3 mg/dl) compared with subjects with no DR (13.2 urea showed higher serum Lp(a) levels, (27.1 ± 2.7 mg/dl) than those with microalbuminuria (16.5 ± 1.6 mg/dl) and normoalbuminuria (14.2 ±1.1 mg/dl, $p < 0.005$)	7
Wen-Jun Tu[23]	China	Cross sectional	2017	377 T2DM patients (182 females – 195 males)	50 (25 – 75)	Continuous and, Q1 vs Q3-4	NA	In this study, was used the canon CR6-45NM ophthalmic digital imaging system and a canon EOS 10D digital camera (Canon, Tokyo, Japan) to take two digital images per eye through a nonpharmacologically dilated pupil. DR was defined as the presence of one or more retinal microaneurysms or retinal blot hemorrhages with or without more severe lesions	Sex, hypertension, history of CVD, smoking, diabetic nephropathy, insulin consumption, sulfonylurea, metformin or lipid-lowering medication, HbA1c, age, diabetes duration, BMI, estimated glomerular filtration rate [eGFR], Hs-CRP	• Patients with Lp(a) (4th quartile) were significantly associated with DR of 5.15 (95% CI, 2.78–9.55; $p < 0.001$) and vision-threatening DR (VTDR) of 5.32 (95% CI, 2.92–10.15; $p < 0.001$) compared with patients with lower concentrations of both factors	8

(continued)

Table 2. (continued)

First author	Country	Type of study	year	Study participation	Mean age	Lp(a) presentation	Follow up duration	Definition of diabetic retinopathy	Variable adjustment	Mean outcomes	Quality score
Jae-Seung Yun[14]	Korea	Cohort	2016	556 T2DM patients without DR (320 females – 236 males)	50(25 - 75)	Q4 vs Q1	11	After maximal dilatation of pupil, retinal images were obtained using a digital fundus camera (TRCNW6S, TOPCON, Japan) equipped with a nikon D-80 digital camera (Nikon, Tokyo, Japan), and digital fundus images were obtained from all participants. For each of the participants, one 45^0 digital retinal images centered on the fovea was obtained per eye (2 images per person in total). The comprehensive eye examination frequency was determined by the ophthalmologist depending on the severity of the diabetic retinopathy. The severity of DR was categorized according to the international clinical diabetic retinopathy severity scales into 5 categories as nondiabetic retinopathy	Sex, age, diabetes duration, hypertension, cardiovascular disease history, smoking, body mass index, diabetic nephropathy, estimated glomerular filtration rate, Lp(a) corrected LDL-C, use of insulin, sulfonylurea, metformin, ACEI/ARBs, statin, and fenofibrate, mean HbA1c, lipoprotein(a)	• The development of DR was significantly associated with the serum Lp(a) level (HR 1.57, 95% CI [1.11–2.24]; $p = 0.012$, the patient group with the highest quartile range of lipoprotein (a) and mean had an HR of 5.09 (95% CI [2.63–9.84]; $p < 0.001$) for	9
Giulia malaguarnera[19]	Italy	Cross sectional	2013	145 T2DM patients (82 females- 63 males)	66 ± 12	Continuous	NA	Assessment of DR was performed by ophthalmoscopy and/or biomicroscopy through dilated pupils by a retinal specialist, and fluorescein angiography was obtained when indicated. Examination of the retina was done through dilated pupils to determine the level of nonproliferative DR or proliferative DR. DR was graded as no retinopathy and minimum, moderate, or severe retinopathy as published elsewhere	Diastolic blood pressure, systolic blood pressure, waist-to-hip ratio, hip circumference, waist circumference, body mass index, smokers/no smokers, age, sex, mean HbA1c, fasting plasma glucose, apolipoprotein B, apolipoprotein A1, triglycerides, LDL-C, HDL-C, cholesterol total	• Patients with retinopathy had significantly higher levels of Lp(a) than patients without retinopathy ($p < 0.001$)	8

(continued)

Table 2. (continued)

First author	Country	Type of study	year	Study participation	Mean age	Lp(a) presentation	Follow up duration	Definition of diabetic retinopathy	Variable adjustment	Mean outcomes	Quality score
Mohamed M. Awad[42]	Egypt	Cross sectional	2017	90 T2DM patients (57 females- 33 males)	55± 8	Continuous	NA	In patients with retinopathy, positive correlations were observed between serum lipoprotein(a) levels and total cholesterol, serum triglycerides and serum LDL-C ($r = 0.52$ $p < 0.001$, $r = 0.55$ $p < 0.001$and $r = 0.68$ $p < 0.001$, respectively)	Age, sex, mean HbA1c, fasting plasma glucose, apolipoprotein B, apolipoprotein A1, triglycerides, LDL-C, HDL-C, FPG	• Patients with DR had significantly higher serum lipoprotein(a) levels as compared to patients without DR (74.11 ± 13.14 vs 51.23 ± 20.63 $p < 0.001$)	-

Abbreviations: NS: non-significant, DRP: diabetic retinopathy, NDRP: None diabetic retinopathy, CI: confidence interval, OR: odds ratio, T2DM: Type 2 Diabetes Mellitus, HDL: high-density lipoprotein, FBG: Fasting Blood Glucose, BUN: blood urea nitrogen, Lp: Lipoprotein, Apo: Apolipoprotein, Hb: hemoglobin, NA: not applicable, NR: normal retina, BMI: body mass index, Cr: creatinine, AER: albumin excretion rate, DBP: diastolic blood pressure, DM: diabetes mellitus, baPWV: brachial ankle pulse-wave velocity, HbA1c: glycosylated hemoglobin, PDR: proliferative diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy, DR: diabetic retinopathy, Q: quartile, AR: active retinopathy.

oxygen species (ROS) and inflammation of the vascular wall.[28,29] It has also been related to an endothelial malfunction.[30] It was suggested that increased Lp(a) levels might lead to DR by damaging the microcirculation.[31] Also, modulated and extravascular plasma lipoproteins are found to predispose DM patients to retinopathy.[32] Second, lipid peroxidation products activate the canonical wingless-type MMTV integration site (WNT) pathway via oxidative stress, which significantly increases the chance of developing retinal diseases.[33] Third, regions that contain oxidized LDL(Ox-LDL) in atherosclerotic lesions are more susceptible to expressing endoplasmic reticulum (ER) stress markers and ORP150 chaperons. Ox-LDL could harm many cells, including vascular and neural cells, and hence may lead to retinal injury. Fourth, Lp(a) plays a significant role in the activation of acute inflammation, and circulating markers of inflammation can be associated with more severe diabetic retinopathy.[34] Fifth, the prothrombotic properties of LP(a) might also play a role in promoting retinal damage. Lp(a) is a famous atherogenic marker with an excessive homology with plasminogen and anti-fibrinolytic properties. Excessive LP(a) levels have been considered an independent risk factor for atherogenic cardiovascular complications in patients with diabetes and healthy individuals.[35] Sixth additionally, cholesterol accumulation is promoted by LP(a) in macrophages, which shapes foam cells.[36] Also, LP(a) interact with other lipid variables to stimulate the protease region of apo(a), thereby subsequently causing atherothrombosis.[37] Laboratory and clinical evidence showed that in addition to microvascular changes, inflammation, and retinal neurodegeneration may contribute to diabetic retinal damage in the early stages of DR.

On the other hand, some research opposes the existence of an association between Lp(a) and retinopathy. In Deepa et al. study, 725 South Indian T2DM patients were observed to determine a relationship between LP(a) and diabetes complications. However, despite the increased level of LP(a) in patients with coronary artery disease and nephropathy, no association was found between LP(a) and DR. One of the reasons for this result is the small sample size of this study.[16] In addition, a cross-sectional study by Ergun et al. demonstrated that no difference in levels of serum LP(a) was found between patients with none proliferative DR and proliferative diabetics, thus if there is a positive relationship between LP(a) levels and proliferative DR among different patients, it might be due to the genetic heterogeneity.[18]This can be explained by the classification of retinopathy, type of diabetes, or ethnic groups in each study.

To the best of our knowledge, this study is the first systematic review to gather current evidence on the relationship between LP(a) level and DR in patients with T2DM. The critical strengths of the systematic review are detailed as follows: Firstly, research with LP(a) had been summarized exclusively and derived consistent outcomes, further validating the quality of the systematic review. Secondly, using different diabetic retinopathy equivalents in the included studies did not affect the results significantly.

This study has some limitations that should be taken into account. Firstly, there was considerable controversy among the included research. Study characteristics,[7,8,11,13–25] like definitions of diabetic retinopathy, follow-up duration, type of study, study country, and other factors, might significantly contribute to this controversy. Specifically, organic dietary products and medications, including phytosterol,[38,39] flaxseed,[40] L-carnitine,[41] and various lipid-lowering medications[42–44] that were rarely reported in the included articles, may affect LP(a) level. In addition, the final results of diabetic retinopathy should be reported based on the stages of the disease. However, in the mentioned studies, various diabetic retinopathy equivalents were used, and in most of them, the stage of the disease was not reported. Therefore, we have not been able to demonstrate the relationship between lipoprotein(a) and diabetic retinopathy based on the disease stage.

Based on recent studies, LP(a) level could be considered an independent risk factor for DR complications in T2DM patients. However, further studies, especially large-scale prospective cohort research, are needed to determine the pathophysiological logic of this association.

Conclusions

In conclusion, LP(a) has generally shown a relatively strong association with DR. Included studies generally showed that Lp(a) increased the risk of both the development and severity of DR. Moreover, both proliferative and non-proliferative DR could be affected by Lp(a). Based on the included studies, lipoprotein (a) can affect oxidized lipids, vascular tone, and perfusion and also increases oxidative stress via the production of reactive oxygen species and inflammation across the vascular wall. Further large-scaled observational studies are required to confirm the association between Lp(a) and DR and elucidate the underlying mechanisms.

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