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Original Research Article

A prospective study of serum lipids and the risk of diabetic retinopathy in type 1 diabetes

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ABSTRACT

Background: Diabetic retinopathy (DR) remains a leading cause of vision loss among individuals with type 1 diabetes, yet factors beyond hyperglycemia that contribute to its onset and progression are not fully understood. Dyslipidemia has been proposed as a modifiable risk factor, but evidence has been inconsistent
Methods: This prospective cohort study investigated the relationship between serum lipid levels and the risk of incident and progressive DR in 1,360 participants with type 1 diabetes, aged 14–38 years, followed for a mean of 6.2 years. Participants were stratified into primary prevention and secondary intervention groups and underwent annual fasting lipid measurements and standardized retinal photography, with outcomes graded according to the early treatment diabetic retinopathy study (ETDRS) scale.
Results: During follow-up, 312 new cases of DR, 286 cases of DR progression, and 94 cases of proliferative DR were identified. Higher LDL cholesterol and elevated total-to-HDL cholesterol ratio were significantly associated with incident DR (HR 2.68 and 3.05, respectively, highest vs. lowest quintile), while triglycerides and total-to-HDL cholesterol ratio predicted disease progression (HR 2.12 and 1.95, respectively). Associations with proliferative DR were attenuated after adjustment for glycemic control. HDL cholesterol showed no independent effect.
Conclusions: These findings suggest that lipid abnormalities contribute primarily to the early development and progression of DR rather than proliferative disease. Given that dyslipidemia is a modifiable risk factor, early identification and treatment may reduce the burden of vision loss in type 1 diabetes. Lipid management, alongside strict glycemic control, should be considered in preventive ophthalmic care.

Keywords: Diabetic retinopathy, Type 1 diabetes, Dyslipidemia

INTRODUCTION

Diabetic retinopathy (DR) is one of the most common microvascular complications of type 1 diabetes and remains a major cause of visual impairment among adults worldwide.[1] The condition develops as a result of chronic damage to small retinal blood vessels, which can lead to microaneurysms, hemorrhages, vascular leakage, and ultimately vision loss. With the growing number of people living with diabetes, the global burden of DR continues to rise, making it a significant public health concern.[2]

Although long-term high blood sugar is well recognized as the strongest driver of DR development, it does not fully explain why some patients develop sight-threatening complications earlier than others, even when glycemic

control appears similar.[3] This suggests that other systemic factors may play a role in the onset and progression of DR. Among these, abnormalities in blood lipids have attracted considerable attention. Elevated cholesterol and triglyceride levels are known to cause blood vessel injury through oxidative stress and endothelial dysfunction, which may in turn weaken the blood retinal barrier and promote retinal leakage.[4]

Several observational studies have examined the link between serum lipids and diabetic retinopathy, but their findings have not been consistent. Some reported strong associations between high levels of low-density lipoprotein (LDL) cholesterol or triglycerides and the presence of retinal hard exudates and macular edema while others found little or no relationship after adjusting for blood glucose control.[5] These conflicting results highlight the need for well-designed prospective studies that can determine whether lipid changes precede the onset of retinopathy.

Prospective evidence is limited, especially in people with type 1 diabetes. Much of the existing research comes from cross-sectional studies, which can identify associations but cannot establish cause and effect. However, understanding whether serum lipids predict the development of DR is clinically important because dyslipidemia is a modifiable risk factor. If certain lipid fractions are shown to increase the risk of retinopathy, early identification and treatment may help reduce the burden of vision loss among patients with diabetes.[6,7]

The aim of this study was therefore to prospectively evaluate the relationship between serum lipid levels and the risk of diabetic retinopathy in individuals with type 1 diabetes. We focused on common lipid measures total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and the ratio of total to HDL cholesterol and examined whether long-term exposure to higher levels was associated with an increased risk of developing or progressing DR, independent of other known risk factors such as blood sugar control, age, and smoking. We hypothesized that higher LDL cholesterol, triglycerides, and total-to-HDL cholesterol ratio would be associated with a greater risk of DR.

METHODS

Study design and participants

We carried out a prospective cohort study to evaluate the relationship between serum lipids and the risk of diabetic retinopathy in individuals with type 1 diabetes. A total of 1,360 participants with type 1 diabetes, aged between 14 and 38 years, were enrolled from multiple diabetes centers across North America. Participants had a known duration of diabetes ranging from 1 to 15 years at baseline.

Two subgroups were defined at entry. The primary prevention group included individuals with diabetes for less than 5 years, no clinical retinopathy on fundus photography, and no history of significant kidney disease. The secondary intervention group included patients with 1-15 years of diabetes, mild to moderate non-proliferative retinopathy, and no advanced kidney disease.

Exclusion criteria were very high baseline cholesterol (above 3 standard deviations for age and sex), low-density lipoprotein (LDL) cholesterol ≥190 mg/dl, body weight more than 30% above ideal, major cardiovascular disease, or other serious systemic illness.

Participants were followed for an average of 6.2 years (range 3-9 years), with a very high follow-up rate (>97% of scheduled visits completed).

Data collection

At baseline and each annual follow-up, fasting blood samples were collected after at least an 8-hour fast. Serum lipid levels including total cholesterol, HDL cholesterol, and triglycerides were measured using standardized enzymatic methods. LDL cholesterol was calculated with the Friedewald equation. Quality control procedures were in place through national lipid standardization programs.

Glycemic control was assessed by quarterly measurements of HbA1c using high-performance liquid chromatography. At each visit, information on smoking status, age, sex, and duration of diabetes was also recorded.

Retinopathy assessment

Standardized seven-field stereoscopic retinal color photographs were obtained at baseline and every 6 months by trained photographers. Images were graded at a central reading center by masked graders according to the early treatment diabetic retinopathy study (ETDRS) scale.

Retinopathy outcomes included-incident diabetic retinopathy – development of at least mild non-proliferative DR in participants free of retinopathy at baseline, progression of DR – defined as a sustained increase of three or more steps on the ETDRS scale from baseline and proliferative diabetic retinopathy (PDR) – presence of neovascularization or vitreous hemorrhage confirmed by fundus photographs.

Statistical analysis

Lipid levels were divided into quintiles based on baseline distribution. Cumulative mean lipid values were calculated for each participant across follow-up visits and treated as time-varying covariates. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of lipids with each retinopathy outcome.

Models were adjusted in a stepwise fashion.

Model 1

Adjusted for baseline subgroup (primary prevention or secondary intervention) and treatment group.

Model 2

Additionally adjusted for mean HbA1c.

Model 3

Further adjusted for age, sex, smoking status, and duration of diabetes.

Analyses were conducted at the individual level rather than per eye. Participants were censored at the time of outcome, last visit, or development of advanced kidney disease.

A two-sided p value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

At study entry, the mean age of participants was 26.4±6.9 years, with an average diabetes duration of 7.1±4.2 years. About 53% were male, and 18% were current smokers. The mean HbA1c was 8.8±1.5%. Baseline characteristics of the study population according to quintiles of total cholesterol are presented in Table 1.

The mean baseline serum lipid values were-total cholesterol: 174 mg/dl (range 70–310), LDL cholesterol: 108 mg/dl (range 20–235), HDL cholesterol: 51 mg/dl (range 22–101), triglycerides: 83 mg/dl (range 25–690) and total-to-HDL cholesterol ratio: 3.4.

Participants with higher lipid levels tended to be slightly older, had longer diabetes duration, and were more likely to smoke compared to those in lower lipid quintiles.

Lipid levels and incident diabetic retinopathy

During a mean follow-up of 6.2 years, 312 new cases of diabetic retinopathy were identified among participants without retinopathy at baseline. After adjusting for subgroup and treatment assignment, higher levels of total cholesterol and LDL cholesterol were associated with a greater risk of developing DR. Individuals in the highest quintile of LDL cholesterol had nearly 2.7 times the risk of incident DR compared with those in the lowest quintile (HR 2.68; 95% CI, 1.34–5.36; p=0.004).

During follow-up, higher LDL cholesterol and total-to-HDL cholesterol ratio were associated with increased risk of incident DR, while triglycerides and total-to-HDL cholesterol ratio predicted DR progression. These results are summarized in Table 2.

Similarly, a higher total-to-HDL cholesterol ratio was strongly associated with increased DR risk (HR for top versus bottom quintile 3.05; 95% CI, 1.41–6.61). Triglycerides also showed a positive association with incident DR, though the trend was weaker after controlling for HbA1c. HDL cholesterol was not significantly related to DR risk.

Lipid levels and DR progression

Among participants with mild to moderate DR at baseline, 286 showed disease progression by three or more steps on the ETDRS scale during follow-up. Progression was more frequent among those with elevated triglycerides and higher total-to-HDL cholesterol ratio. After full adjustment, the hazard ratio for progression in the highest versus lowest quintile of triglycerides was 2.12 (95% CI, 1.18–3.81; p=0.01). The association for total-to-HDL cholesterol ratio was similar (HR 1.95; 95% CI, 1.06–3.59; p=0.03).

In contrast, total cholesterol and LDL cholesterol were not independently associated with progression once HbA1c was included in the models.

Table 1: Baseline characteristics of participants according to quintiles of total cholesterol.

Characteristic	Quintile 1 (<150 mg/dl)	Quintile 2 (150–165 mg/dl)	Quintile 3 (166–180 mg/dl)	Quintile 4 (181–200 mg/dl)	Quintile 5 (>200 mg/dl)
No. of participants	260	270	270	280	280
Mean age (years)	24.5±6.7	25.8±7.1	26.4±6.9	27.5±7.2	28.2±7.3
Male (%)	55.1	52	50.3	48.9	47
Current smoking (%)	11.2	15.6	18.1	21	24.7
Diabetes duration (years)	6.3±4.0	6.8±4.2	7.1±4.1	7.6±4.3	8.0±4.4
Mean HbA1c (%)	8.5±1.4	8.7±1.5	8.9±1.5	9.0±1.6	9.3±1.7

Table 2: Association of serum lipid levels with diabetic retinopathy outcomes.

Lipid parameter (highest versus lowest quintile)	Incident DR (HR, 95% CI)	DR progression (HR, 95% CI)	Proliferative DR (HR, 95% CI)
Total cholesterol	2.10 (1.15–3.85)*	1.25 (0.74–2.12)	1.18 (0.56–2.45)
LDL cholesterol	2.68 (1.34–5.36)*	1.32 (0.71–2.47)	1.11 (0.49–2.48)
HDL cholesterol	0.91 (0.52–1.60)	0.88 (0.50–1.56)	0.79 (0.41–1.54)
Total-to-HDL cholesterol ratio	3.05 (1.41–6.61)*	1.95 (1.06–3.59)*	1.36 (0.63–2.95)
Triglycerides	1.78 (0.92–3.43)	2.12 (1.18–3.81)*	1.42 (0.66–3.04)

*P<0.05

Table 3: Summary of main findings on serum lipids and diabetic retinopathy in type 1 diabetes.

Lipid parameter	Incident DR	DR progression	Proliferative DR
Total cholesterol	↑ Risk (significant)	No independent effect	No significant effect
LDL cholesterol	↑ Risk (significant)	No independent effect	No significant effect
HDL cholesterol	No effect	No effect	No effect
Total-to-HDL cholesterol ratio	↑ Risk (strongest predictor)	↑ Risk (moderate)	Weak, not significant
Triglycerides	Borderline association	↑ Risk (significant)	No significant effect

Lipid levels and proliferative diabetic retinopathy

During follow-up, 94 participants developed proliferative DR. Initial models suggested higher triglycerides and higher total-to-HDL cholesterol ratio were linked with increased risk of PDR. However, after adjusting for HbA1c and other covariates, these associations were attenuated and were no longer statistically significant.

To provide a concise overview, Table 3 summarizes the main findings across all lipid parameters and retinopathy outcomes.

DISCUSSION

In this prospective cohort of individuals with type 1 diabetes, we observed that higher levels of certain serum lipids were associated with an increased risk of diabetic retinopathy. Elevated LDL cholesterol and a higher total-to-HDL cholesterol ratio were significant predictors of incident DR, while triglycerides and total-to-HDL cholesterol ratio were linked with progression of established retinopathy. However, we did not find a consistent independent relationship between lipid parameters and proliferative diabetic retinopathy after adjustment for glycemic control and other risk factors.

Our results support the biological plausibility of a role for dyslipidemia in the pathogenesis of DR. Elevated cholesterol and triglycerides are known to impair endothelial function, promote oxidative stress, and disrupt the integrity of the blood retinal barrier, which may lead to vascular leakage and retinal exudation.[8] This mechanism may explain why lipid abnormalities were most strongly associated with the earlier stages of retinopathy, such as development of hard exudates and worsening of background DR, rather than with later proliferative disease.

Several earlier studies have investigated this relationship, but findings have been inconsistent. Cross-sectional data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) suggested that higher cholesterol was related to retinal hard exudates.[9] Similarly, the ETDRS reported that elevated serum lipids were associated with more severe hard exudate formation.[10] In contrast, other prospective analyses failed to demonstrate independent associations once HbA1c and other covariates were considered.[11] Our findings, showing persistent associations for LDL cholesterol, triglycerides, and the total-to-HDL ratio even after adjusting for glycemia, add prospective evidence to this debate.

An important observation from our study is that lipid abnormalities were more predictive of incident DR and its early progression rather than of proliferative disease. One explanation may be that the pathogenesis of PDR is driven more strongly by long-term hyperglycemia and ischemia than by lipid-related mechanisms.[12] Another possibility is that our follow-up duration, although substantial, was not long enough to capture a larger number of PDR cases, thereby limiting statistical power.

The clinical implications of these findings are noteworthy. Dyslipidemia is a modifiable risk factor, and lipid-lowering therapy is already recommended for cardiovascular risk reduction in patients with diabetes.[13] Our results suggest that lipid control may also have ophthalmic benefits by reducing the risk of retinopathy onset and progression. This dual benefit further supports early screening for dyslipidemia and aggressive treatment when indicated in young patients with type 1 diabetes.

Strengths and limitations

The strengths of this study include its prospective design, large sample size, long follow-up, repeated measurements of both lipids and HbA1c, and standardized grading of retinal photographs. These features reduce the likelihood of bias and provide a reliable assessment of temporal relationships.

However, certain limitations must be acknowledged. First, participants were relatively healthy volunteers with type 1 diabetes, which may limit the generalizability of the findings to all patients. Second, individuals with very high cholesterol levels were excluded at baseline, which could have underestimated the strength of the associations. Third, although we adjusted for major confounders, residual confounding by unmeasured factors cannot be ruled out.

Finally, newer imaging techniques such as optical coherence tomography were not available at the time of data collection, which may have limited sensitivity for detecting subtle retinal change.

CONCLUSION

In summary, this prospective study demonstrates that higher LDL cholesterol, triglycerides, and total-to-HDL cholesterol ratio are associated with an increased risk of diabetic retinopathy in type 1 diabetes, particularly with respect to disease onset and progression. These findings highlight the importance of lipid control, in addition to glycemic management, in reducing the risk of vision-threatening complications. Future studies with longer follow-up and newer retinal imaging modalities are warranted to further clarify these relationships.

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