HHS Public Access

Author manuscript

JAMA Ophthalmol. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

JAMA Ophthalmol. 2015 May 1; 133(5): 503–510. doi:10.1001/jamaophthalmol.2014.5108.

Serum Lipids and Proliferative Diabetic Retinopathy and Macular Edema in Persons with Long Term Type 1 Diabetes: The Wisconsin Epidemiologic Study of Diabetic Retinopathy

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Abstract

Importance—Total serum and high-density lipoprotein cholesterol have been considered risk factors for severe vascular outcomes in persons with type 1 diabetes.

Objective—Examine the long term relationships between these two serum lipids and the incidence and prevalence of proliferative diabetic retinopathy and macular edema.

Design, Setting, and Participants—903 persons with younger-onset type 1 diabetes who participated in the Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Exposure(s)—Serum total and high-density cholesterol and history of statin use over the course of 5 visits spanning approximately 30 years (1984–2014).

Main Outcome Measure(s)—Prevalence and incidence of proliferative diabetic retinopathy and macular edema.

Results—A modest association was found for higher levels of high-density lipoprotein cholesterol and decreased prevalence of proliferative diabetic retinopathy (odds ratio per 10

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CONFLICT OF INTEREST DISCLOSURES: Drs. B. E. K. Klein and R. Klein report grants from the National Institutes of Health and Research to Prevent Blindness during the conduct of the study.

DATA ACCESS STATEMENT/ANALYSIS: Ms. Howard had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Ms. Myers and Ms. Howard conducted and are responsible for the data analysis.

DISCLAIMER: The content is solely the responsibility of the authors and does not necessarily reflect the official views of the National Eye Institute or the National Institutes of Health.

MEETING PRESENTATION: An abstract of this study was presented at the 2014 Annual Meeting of the Association for Research and Vision in Ophthalmology (ARVO), Orlando, Florida, USA, May 4–8, 2014.

AUTHOR CONTRIBUTIONS: Conception and design (B. E. K. Klein), acquisition of data (B. E. K. Klein, R. Klein), analysis or interpretation of data (all authors), drafting of the manuscript (B. E. K. Klein), critical revision of the manuscript for important intellectual content (Myers, Howard, R. Klein), statistical analysis (Myers, Howard), obtaining funding (B. E. K. Klein, R. Klein), supervision of the study (B. E. K. Klein, R. Klein).

mg/dL 0.87, 95% confidence interval 0.82–0.93), adjusting for duration of diabetes, glycosylated hemoglobin A1c, statin use, and end stage renal disease. While adjusting for covariates, no associations of serum total or high density lipoprotein cholesterol and incident proliferative diabetic retinopathy or macular edema, nor of statin use with decreased incidence of proliferative diabetic retinopathy or macular edema, were identified.

Conclusions and Relevance—Over the course of long duration diabetes, during a time of changing medical care, there appeared to be little effect of serum lipids or statins on incidence of proliferative diabetic retinopathy and macular edema.

INTRODUCTION

Proliferative diabetic retinopathy and macular edema are important causes of decreased vision in persons with type 1 diabetes.[1] Serum lipids have been found to be associated with the incidence and progression of lesions of diabetic retinopathy[2] and macular edema[3] although in some studies the associations were no longer observed after adjustment for important covariates.[4] Long-term estimates of these relationships are uncommon, as type 1 diabetes is an uncommon disease and systematic long term follow-up data of persons in the general population with this condition are usually not available. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) has documented the presence and severity of retinal lesions associated with diabetes over more than 30 years during a period of change in treatment and levels of glycemia, blood pressure, and serum lipids.[5–8] In this report, we investigated the prevalence and incidence of proliferative diabetic retinopathy (PDR) and macular edema in the WESDR cohort over the course of five examinations spanning approximately 30 years.

METHODS

Subjects

The study group for this investigation consisted of all persons with type 1 diabetes who received primary care in an 11-county area in southern Wisconsin between 1979 and 1980.[9–16] Of the 1210 such persons, 996 participated in the baseline examination (1980–1982),[9] 903 participated in the 4-year follow-up (1984–1986),[12] 816 participated in the 10-year follow-up (1990–1992),[13] 667 participated in the 14-year follow-up (1994–1996),[14] 567 participated in the 20-year follow-up (2000–2001),[17] 520 participated in the 25-year follow-up (2005–2007),[16] and 335 participated in the 32-year follow-up (2012–2014). Reasons for nonparticipation and comparisons between participants and nonparticipants at each examination have been presented elsewhere.[9–14,16–18] Analyses in this report are limited to persons who completed at least one examination phase beginning at the 4-year follow-up, had information regarding retinopathy level, and had serum total and high-density lipoprotein cholesterol measured at the time of their examination. Data from the 20-year follow-up examination were excluded because the determination of the outcome variables (PDR and macular edema) is not comparable to that of the other examinations.

Procedures

The examinations were performed in a mobile examination van, or clinic near the participant's place of residence, or in the participant's residence. Informed consent was obtained from participants before each examination, and all examinations followed a similar protocol that was approved by the institutional Human Subjects Committee of the University of Wisconsin and which conformed to the tenets of the Declaration of Helsinki.

The study examinations and interviews were conducted by trained examiners. Quality control was monitored throughout each study examination phase. The pertinent parts of the ocular and physical examinations included measuring height and weight, measuring blood pressure,[19] dilating the pupils, and taking stereoscopic color fundus photographs of seven standard fields.[20,21] Due to funding constraints, there were no photographs taken at the 20-year follow-up examination. A structured interview was conducted that included questions about medication use, history of kidney transplant and dialysis, and smoking history. If there was any doubt regarding history of medication use, it was verified by a physician's report. An aliquot of whole blood was used for determination of the glycosylated hemoglobin (A1c) level using affinity chromatography (Isolab, Inc., Akron, OH). The normal range for A1c was 4.6% to 7.9%. Its intra-assay coefficient of variation was 2.4%. Serum was used to measure total and HDL cholesterol.[22,23]

Definitions

For each eye, the maximum grade of diabetic retinopathy in any of the seven standard photographic fields was determined for each of the lesions using the Early Treatment Diabetic Retinopathy Study (ETDRS) classification scheme.[13,24] Proliferative diabetic retinopathy was defined as having ETDRS severity level 60 or greater in either eye. Macular edema was defined as retinal thickening in the macular area in either eye according to the ETDRS classification scheme.[25]

Because serum cholesterol was not measured at the baseline examination, prevalence of PDR and macular edema was defined at each examination beginning at the second WESDR examination in 1984–1986 (and excluding the fifth examination in 2000–2001). Incidence of PDR and macular edema were defined, beginning at the second WESDR examination and excluding the fifth, as the presence of PDR or macular edema in either eye in an individual who had been free of PDR or macular edema at all previous examinations.

Age was defined as the participant's age at the time of each examination. Age at diagnosis of diabetes was defined as the participant's age at the time the diagnosis was first recorded by a physician on the patient's chart or in a hospital record. The duration of diabetes was defined as the period between the participant's age at diagnosis and his or her age at each WESDR examination. Systolic and diastolic blood pressures were defined as the average of the last two of three measurements taken obtained according to the protocol of the Hypertension Detection and Follow-up Program.[19] Body mass index was defined as the participant's weight in kg divided by the height in m^2. End stage renal disease (ESRD) was defined as participant report of receiving dialysis or a kidney transplant. Statins are

competitive inhibitors of hydroxymethylglutaryl-coenzyme A reductase. Statin use is current use at the time of each study examination.

Statistical Analysis

Cross-sectional analyses evaluated associations of serum total and HDL cholesterol to the prevalence of PDR and macular edema using proportional odds models.

Incidence analyses examined the associations of total and HDL cholesterol to the incidence of PDR and macular edema. Multi-level modeling was used to account for the varying follow-up times between examinations (six years between the 1984–1986 and 1990–1992 examinations, four years between the 1990–1992 and 1994–1996 examinations, 11 years between the 1994–1996 and 2005–2007 examinations, and 7 years between the 2005–2007 and 2012–2014 examinations). For incidence analyses, duration of diabetes was used as the time scale, and the baseline hazard was assumed to be piecewise constant with duration of diabetes categorized as <20 years, 20–29 years, and >30 years of duration. Duration of diabetes was not reported as a covariate in incidence models because it was used as the time scale. Hazard ratio (HR) estimates were calculated by exponentiation of estimated coefficients. The PROC GENMOD and PROC NLMIXED of SAS version 9.1 (Cary, NC) were used for the cross-sectional and incidence analyses, respectively.

Multivariable analyses were performed adding adjustment variables in a stepwise manner. Initial prevalence and incidence models included serum total or HDL cholesterol and duration of diabetes. Next, A1c, statin use, and ESRD (in prevalence models) were sequentially added to each model to evaluate the effect of each covariate on each retinal outcome as well as on each lipid/retinal outcome relationship. ESRD was not included as a covariate in incidence models because too few individuals with ESRD were at risk for incidence of PDR or macular edema. However, because ESRD in persons with diabetes is strongly associated with severity of retinopathy and with serum lipids, we also evaluated the relationship of lipids to retinal outcomes in the subset of the cohort without ESRD.

RESULTS

Participant Characteristics

There were 819 participants (400 women and 419 men) who contributed 2319 person-visits to analyses for the prevalence of PDR or macular edema. There were 520 participants (269 women and 251 men) who contributed 1146 person-visits to analyses for the incidence of PDR or macular edema. The mean durations of diabetes, included in the prevalence and incidence analyses, respectively, was 27.7 years and 22.8 years, mean A1c was 8.7% and 8.8%, and regular statin use was reported by 20.5% and 7.4% of participants over all person-visits (Table 1). The estimated prevalence of PDR was 41.0% per person-visit and 23.8% for macular edema. The estimated incidence of PDR was 1.21% per person-year and 0.77% for macular edema.

The proportion of persons reporting statin use increased at each visit, with a marked increase reported at the last two examinations. Reported statin use was associated with lower total cholesterol levels (162.7 mg/dL vs. 194.6 mg/dL, respectively, for statin users vs non-users,

P<0.01 adjusting for age). However, HDL cholesterol differed little by statin use status over all visits (55.1 mg/dL vs. 51.0 mg/dL for users vs. non-users, P=0.75 adjusting for age).

Associations of Lipids with Prevalent PDR and ME

A higher serum total cholesterol level was associated with a higher prevalence of PDR (odds ratio [OR] 1.06, 95% confidence interval [CI] 1.02–1.10; Table 2). Adding A1c to the model slightly decreased the OR for total cholesterol (1.03, 95% CI 0.99–1.07). Adding statin use and ESRD to the model had little effect on the OR for serum total cholesterol (1.03, 95% CI 0.99–1.08). This series of analyses was repeated for serum HDL cholesterol (Table 2). Higher HDL cholesterol level was associated with decreased odds of PDR when including A1c in the model (OR 0.86, 95% CI 0.81–0.92) and also when further including statin use and ESRD (OR 0.87, 95% CI 0.82–0.93).

Applying a similar modeling approach (Table 2), we found that serum total cholesterol was directly associated with increased odds of prevalent macular edema (OR 1.08, 95% CI 1.03–1.12) adjusting for age and serum HDL cholesterol was inversely associated with prevalent macular edema when adjusting for duration of diabetes, A1c, and statin use (OR 1.04, 95% CI 0.99–1.09 for serum total cholesterol; OR 0.91, 95% CI 0.85–0.98 for HDL cholesterol), but not in the full model including ESRD (OR 0.94, 95% CI 0.87–1.01). After including ESRD in each model, only serum HDL cholesterol remained associated with a decreased prevalence of PDR (OR=0.87, 95% CI 0.82–0.93).

Associations of Lipids with Incident PDR and ME

Serum total cholesterol was associated with an increased risk of incident PDR (hazard ratio [HR] per 20 mg/dL 1.13, 95% CI 1.06–1.21) and serum HDL cholesterol was associated with a decreased risk of incident macular edema (HR per 10 mg/dL 0.83, 0.71–0.96; Table 3). However, neither of these associations remained after further adjustment for A1c and statin use (Table 3).

Effect of Mortality

In order to examine the potential effect of mortality on the lipid analyses, we examined the hazard of death associated with total and HDL cholesterol levels. The HR for total cholesterol was 0.96 (95% CI 0.76–1.22) and for HDL cholesterol it was 0.88 (95% CI 0.69–1.13).

Effect of ESRD

End stage renal disease is often associated with lipid levels and macrovascular complications of diabetes. In this study cohort, across all visits, serum total cholesterol and HDL cholesterol levels were not higher in those with ESRD compared to those without (188.2 mg/dL vs. 186.9 mg/dL respectively for serum total cholesterol and 51.9 mg/dL vs. 51.2 mg/dL respectively for serum HDL cholesterol), adjusting for statin use. However, adjusting for cholesterol levels, individuals with ESRD were more likely to currently take a statin (P<0.01) than those without ESRD. When ESRD status was considered in our models, it did not materially affect the strength of the association of the lipids to prevalence of PDR

and macular edema. End stage renal disease itself was associated with prevalent retinal outcomes.

There were 217 individuals with ESRD in the prevalence analyses and 10 individuals with ESRD in the incidence analyses. When the previous analyses were rerun excluding these individuals, serum total cholesterol was directly associated with an increased prevalence of macular edema but not PDR, and HDL cholesterol was inversely associated with risk of both macular edema and PDR, adjusting for duration of diabetes, A1c, and statin use. After excluding individuals with ESRD, no associations were found between serum total or serum HDL cholesterol and incident PDR or macular edema.

COMMENT

This report provides long term follow-up data on the association between measures of serum lipids and prevalent and incident PDR and macular edema. While the outcomes for prevalence relationships of total and HDL cholesterol level accounting for A1c are modest, neither serum lipid is associated with incidence of either retinal outcome. There are limited data supporting an independent role of serum lipids on microvascular complications of diabetes.[26–28] We have reported a cross sectional association between retinal hard exudates and total cholesterol in a previous publication.[29] We are uncertain of the reason for the differences but they may be related to the fact that our prior study was on a small number of subjects (n=299) and also that, being a cross sectional relationship, the temporal order of the association could not be determined. Romero and colleagues[28] reported that high levels of low-density lipoprotein cholesterol were associated with incident diabetic retinopathy in 112 persons with type 1 diabetes who were followed for 15 years but an association with HDL cholesterol was not identified. Information on incidence of PDR or macular edema with regard to serum lipids were not presented (PDR was an uncommon outcome) so it is not possible to directly compare those results with ours. Cetin and colleagues[30] examined the relationships of total serum cholesterol, low-density lipoprotein cholesterol, and triglycerides with severity of diabetic retinopathy in a university based clinical chart review of 191 patients. No associations were identified. While ours is a cohort study and our longitudinal data provide a potentially powerful model to detect associations, our results suggest a modest effect of serum lipids on PDR and macular edema. To evaluate the possibility that selective mortality affected our results, we examined the association of serum total and HDL cholesterol on survival. In these data we did not observe an effect, so there is doubt that this has caused a spuriously diminished relationship between the lipid levels and retinal outcomes.

The effects of statins on lipid levels are well established, and the resultant decrease in risk of macrovascular disease associated with these medications is also well documented.[31] While we found that serum total cholesterol was lower in the presence of statin use,[8] we found no evidence to support a beneficial effect of statins on microvascular disease as reflected in retinopathy in our study; another bit of evidence compatible with the interpretation of limited effect of serum total and HDL cholesterol on the retinopathy endpoints. We also note that we did not identify an effect of the presence of ESRD on the relationship of serum lipids to the retinal endpoints.

In the current analyses of the WESDR data, the presence of ESRD was a stronger correlate of prevalent PDR and macular edema than serum lipids, A1c, or duration of diabetes. This may reflect common risk indicators and risk factors (e.g., markers of oxidation, inflammation, endothelial dysfunction, uric acid, cytokines, advanced glycation endproducts) as well as effects of other metabolic changes and medications to which persons with ESRD are exposed.[32–34] We were unable to address the possible effects of these exposures as well as potential effects of other unmeasured confounders.

While long term follow-up permitted the opportunity to examine relationships of serum total and HDL cholesterol to severe retinal outcomes over the course of long duration type 1 diabetes, this occurred during a time of great change in the medical care of persons with diabetes. This may have influenced our findings in that there has been a decreasing risk of progression of diabetic retinopathy to the severe lesions of interest in this paper. In addition, treatment of triglyceride levels with fenofibrate in patients with a background of statin use has been found to decrease the risk of progression of diabetic retinopathy.[35] It was not possible to test whether there might be synergy of high triglyceride levels with cholesterol as triglycerides were measured only at the fifth WESDR examination, nor could effect of fenofibrate on the retina in WESDR be measured as there were too few users of this medication in the cohort. Because of the many differences in lifestyle and health care among subjects in these types of studies, it is not possible to reconcile disparate findings. Another limitation of our findings is that this cohort had little racial/ethnic diversity. If race/ethnicity influences the strength of lipid risk factors for PDR and macular edema, our data would be primarily relevant to a white European derived American population.

SUMMARY/CONCLUSION

We have found modest associations between total serum and HDL cholesterol and the prevalence of PDR and macular edema, two vision threatening complications of diabetes, in persons with long duration type 1 diabetes. The lack of an observed association of lipids and the incidence of these severe retinal outcomes is compatible with the possibility that these serum lipids are not important in the etiology of PDR and macular edema.

Acknowledgments

FUNDING SOURCES AND ROLE OF SPONSORS: This research was supported by the National Institutes of Health grant EY016379 (R Klein, BEK Klein) and an unrestricted grant from Research to Prevent Blindness, New York, NY. The organizations that provided funding were in no way involved in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

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JAMA Ophthalmol. Author manuscript; available in PMC 2016 May 01.

Table 1

Characteristics of the Population of the Wisconsin Epidemiologic Study of Diabetic Retinopathy at Each Examination[a]

Prevalence analyses[b]						
	WESDR 2 1984–1986 (N=392)	**WESDR 3 1990–1992 (N=686)**	**WESDR 4 1994–1996 (N=513)**	**WESDR 6 2005–2007 (N=422)**	**WESDR 7 2012–2014 (N=306)**	**Overall (N=2319)**
Covariate	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**
Age, y	33.0 ±12.8	37.3 ±11.8	40.9 ±10.7	50.0 ±9.5	56.0 ±8.9	42.1 ±13.4
Diabetes duration, y	18.5 ±10.1	22.8 ±9.3	26.4 ±8.2	35.8 ±7.1	41.8 ±6.4	27.7 ±11.5
Glycosylated hemoglobin, %	9.5 ±1.9	9.3 ±1.6	8.9 ±1.5	7.6 ±1.4	7.8 ±1.2	8.7 ±1.7
Systolic blood pressure, mmHg	122.2 ±17.4	125.9 ±18.5	126.6 ±18.8	133.0 ±20.5	135.9 ±19.1	128.1 ±19.4
Diastolic blood pressure, mmHg	76.8 ±10.7	76.2 ±11.3	74.8 ±10.6	73.3 ±10.3	72.7 ±9.1	75.0 ±10.7
Body mass index, kg/m^2	24.7 ±4.0	25.8 ±4.0	26.7 ±4.4	28.7 ±5.5	29.0 ±5.6	26.8 ±4.9
Serum total cholesterol, mg/dL	202.8 ±50.4	197.1 ±45.6	196.7 ±42.9	166.9 ±37.9	163.7 ±37.0	188.1 ±46.1
Serum HDL cholesterol, mg/dL	51.0 ±16.0	46.7 ±14.1	49.7 ±14.4	56.6 ±17.5	61.5 ±17.9	51.8 ±16.5
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Sex						
Female	195 (49.7)	331 (48.3)	233 (45.4)	201 (47.6)	154 (50.3)	1114 (48.0)
Male	197 (50.3)	355 (51.7)	280 (54.6)	221 (52.4)	152 (49.7)	1205 (52.0)
Using statins						
No	392 (100.0)	672 (98.0)	478 (93.2)	213 (50.5)	88 (28.8)	1843 (79.5)
Yes	0 (0.0)	14 (2.0)	35 (6.8)	209 (49.5)	218 (71.2)	476 (20.5)
Smoking history						
Never	233 (59.4)	391 (57.0)	296 (57.7)	251 (59.5)	192 (63.0)	1363 (58.8)
Past	78 (19.9)	147 (21.4)	119 (23.2)	118 (28.0)	87 (28.5)	549 (23.7)
Current	81 (20.7)	148 (21.6)	98 (19.1)	53 (12.6)	26 (8.5)	406 (17.5)
End-stage renal disease						
Absent	372 (94.9)	640 (93.3)	464 (90.4)	361 (85.5)	265 (86.6)	2102 (90.6)
Present	20 (5.1)	46 (6.7)	49 (9.6)	61 (14.5)	41(13.4)	217 (9.4)
Prevalent macular edema						
Absent	301 (85.3)	488 (77.0)	365 (75.1)	245 (70.6)	172 (71.1)	1571 (76.2)

Prevalence analyses[b]						
	WESDR 2 1984–1986 (N=392)	WESDR 3 1990–1992 (N=686)	WESDR 4 1994–1996 (N=513)	WESDR 6 2005–2007 (N=422)	WESDR 7 2012–2014 (N=306)	Overall (N=2319)
Covariate	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**
Present	52 (14.7)	146 (23.0)	121 (24.9)	102 (29.4)	70 (28.9)	491 (23.8)
Prevalent PDR						
Absent	277 (70.7)	418 (60.9)	298 (58.3)	218 (51.7)	155 (51.0)	1366 (59.0)
Present	115 (29.3)	268 (39.1)	213 (41.7)	204 (48.3)	149 (49.0)	949 (41.0)

Incidence analyses[c]					
	WESDR 2 1984–1986 (N=262)	WESDR 3 1990–1992 (N=432)	WESDR 4 1994–1996 (N=261)	WESDR 6 2005–2007 (N=191)	Overall (N=1146)
Covariate	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**
Age, y	30.9 ±11.9	35.7 ±11.1	38.6 ±9.6	48.9 ±9.0	37.5 ±12.1
Diabetes duration, y	16.3 ±9.0	21.1 ±8.3	24.0 ±7.0	34.1 ±6.4	22.8 ±9.7
Glycosylated hemoglobin, %	9.4 ±1.8	9.1 ±1.5	8.5 ±1.3	7.5 ±1.3	8.8 ±1.6
Systolic blood pressure, mmHg	119.2 ±15.5	123.4 ±16.3	121.7 ±15.2	130.5 ±18.3	123.2 ±16.6
Diastolic blood pressure, mmHg	76.2 ±10.4	75.6 ±10.4	74.1 ±9.7	73.2 ±9.0	75.0 ±10.0
Body mass index, kg/m^2	24.6 ±4.0	25.7 ±3.8	26.5 ±3.9	28.5 ±5.2	26.1 ±4.3
Serum total cholesterol, mg/dL	195.8 ±45.9	190.2 ±42.2	190.1 ±41.7	170.5 ±40.7	188.2 ±43.4
Serum HDL cholesterol, mg/dL	51.9 ±15.3	47.0 ±14.2	51.1 ±14.4	59.3 ±18.0	51.1 ±15.7
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Sex					
Female	141 (53.8)	217 (50.2)	122 (46.7)	100 (52.4)	580 (50.6)
Male	121 (46.2)	215 (49.8)	139 (53.3)	91 (47.6)	566 (49.4)
Using statins					
No	262 (100.0)	426 (98.6)	252 (96.6)	121 (63.4)	1061 (92.6)
Yes	0 (0.0)	6 (1.4)	9 (3.4)	70 (36.6)	85 (7.4)
Smoking history					
Never	168 (64.1)	261 (60.4)	161 (61.7)	116 (60.7)	706 (61.6)
Past	47 (17.9)	79 (18.3)	56 (21.5)	51 (26.7)	233 (20.3)

Incidence analyses[c]					
	WESDR 2 1984–1986 (N=262)	WESDR 3 1990–1992 (N=432)	WESDR 4 1994–1996 (N=261)	WESDR 6 2005–2007 (N=191)	Overall (N=1146)
Covariate	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**
Current	47 (17.9)	92 (21.3)	44 (16.9)	24 (12.6)	207 (18.1)
End-stage renal disease					
Absent	260 (99.2)	427 (98.8)	259 (99.2)	190 (99.5)	1136 (99.1)
Present	2 (0.8)	5 (1.2)	2 (0.8)	1 (0.5)	10 (0.9)
Prevalent macular edema					
Absent	215 (87.8)	352 (90.0)	190 (90.0)	152 (92.7)	909 (89.9)
Present	30 (12.2)	39 (10.0)	21 (0.0)	12 (7.3)	102 (10.1)
Prevalent PDR					
Absent	183 (75.9)	323 (90.7)	203 (82.9)	151 (88.8)	860 (85.0)
Present	58 (24.1)	33 (9.3)	42 (17.1)	19 (11.2)	152 (15.0)

HDL, high-density lipoprotein; PDR, proliferative diabetic retinopathy; SD, standard deviation; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

[a] Percentages may not always add to 100% due to rounding.

[b] Numbers presented for each examination phase for prevalence analyses are those included in analyses at that visit.

[c] Numbers presented for incidence analyses for each examination phase are those at risk for incidence between the current visit and the consecutive visit (e.g., N=262 at WESDR 2 are those at risk for incidence of macular edema or proliferative diabetic retinopathy between WESDR 2 and WESDR 3).

JAMA Ophthalmol. Author manuscript; available in PMC 2016 May 01.

Table 2

Covariate-Adjusted Associations of Serum Total and High-Density Lipoprotein Cholesterol and the Prevalence of Proliferative Diabetic Retinopathy and Macular Edema

Prevalent PDR	**Model 1**		**Model 2**		**Model 3**		**Model 4**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Serum total cholesterol								
Duration of diabetes	1.04 (1.03, 1.05)	<0.001	1.04 (1.03, 1.05)	<0.001	1.04 (1.03, 1.05)	<0.001	1.04 (1.03, 1.05)	<0.001
Serum total cholesterol per 20 mg/dL	1.06 (1.02, 1.10)	0.002	1.03 (0.99, 1.07)	0.16	1.04 (1.00, 1.09)	0.04	1.03 (0.99, 1.08)	0.13
Glycosylated hemoglobin A1c, per 1%			1.12 (1.06, 1.18)	<0.001	1.12 (1.07, 1.18)	<0.001	1.18 (1.10, 1.26)	<0.001
Using statins (yes vs. no)					1.38 (1.10, 1.73)	0.006	1.28 (1.01, 1.62)	0.04
ESRD status (present vs. absent)							6.52 (4.36, 9.77)	<0.001
Serum HDL cholesterol								
Duration of diabetes	1.04 (1.03, 1.05)	<0.001	1.05 (1.04, 1.06)	<0.001	1.05 (1.03, 1.06)	<0.001	1.04 (1.03, 1.05)	<0.001
Serum HDL cholesterol per 10 mg/dL	0.85 (0.80, 0.91)	<0.001	0.86 (0.81, 0.92)	<0.001	0.86 (0.81, 0.92)	<0.001	0.87 (0.82, 0.93)	<0.001
Glycosylated hemoglobin A1c, per 1%			1.12 (1.07, 1.18)	<0.001	1.13 (1.08, 1.19)	<0.001	1.18 (1.11, 1.26)	<0.001
Using statins (yes vs. no)					1.26 (1.01, 1.57)	0.04	1.19 (0.95, 1.51)	0.14
ESRD status (present vs. absent)							6.50 (4.25, 9.95)	<0.001
Prevalent Macular Edema								
Serum total cholesterol								
Duration of diabetes	1.03 (1.02, 1.04)	<0.001	1.04 (1.03, 1.05)	<0.001	1.03 (1.02, 1.04)	<0.001	1.03 (1.02, 1.04)	<0.001
Serum total cholesterol per 20 mg/dL	1.08 (1.03, 1.12)	0.001	1.04 (1.00, 1.09)	0.07	1.05 (1.00, 1.10)	0.03	1.04 (0.99, 1.09)	0.09
Glycosylated hemoglobin A1c, per 1%			1.12 (1.05, 1.20)	0.001	1.13 (1.06, 1.21)	<0.001	1.16 (1.09, 1.24)	<0.001
Using statins (yes vs. no)					1.26 (0.95, 1.69)	0.11	1.23 (0.92, 1.64)	0.15
ESRD status (present vs. absent)							4.13 (2.89, 5.91)	<0.001
Serum HDL cholesterol								
Duration of diabetes	1.03 (1.02, 1.04)	<0.001	1.04 (1.03, 1.05)	<0.001	1.04 (1.03, 1.05)	<0.001	1.03 (1.02, 1.04)	<0.001
Serum HDL cholesterol per 10 mg/dL	0.90 (0.83, 0.97)	0.005	0.91 (0.84, 0.98)	0.01	0.91 (0.85, 0.98)	0.01	0.94 (0.87, 1.01)	0.09
Glycosylated hemoglobin A1c, per 1%			1.14 (1.07, 1.21)	<0.001	1.15 (1.08, 1.22)	<0.001	1.18 (1.10, 1.25)	<0.001
Using statins (yes vs. no)					1.15 (0.87, 1.53)	0.33	1.16 (0.87, 1.54)	0.32
ESRD status (present vs. absent)							4.04 (2.80, 5.82)	<0.001

CI, confidence interval; ESRD, end stage renal disease; HDL, high-density lipoprotein; OR, odds ratio; PDR, proliferative diabetic retinopathy.

Model 1 includes duration of diabetes and serum total cholesterol (for analyses of total cholesterol) or serum HDL cholesterol (for analyses of HDL cholesterol).

Model 2 includes all variables in Model 1 plus glycosylated hemoglobin A1c.

Model 3 includes all variables in Model 2 plus statin use.

Model 4 includes all variables in Model 3 plus ESRD status.

JAMA Ophthalmol. Author manuscript; available in PMC 2016 May 01.

Table 3

Covariate-Adjusted Associations of Serum Total and High-Density Lipoprotein Cholesterol and the Incidence of Proliferative Diabetic Retinopathy and Macular Edema

Incident PDR	**Model 1**		**Model 2**		**Model 3**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Serum total cholesterol						
Serum total cholesterol, per 20 mg/dL	1.13 (1.06, 1.21)	<0.001	1.02 (0.95, 1.09)	0.63	1.02 (0.95, 1.09)	0.66
Glycosylated hemoglobin A1c, per 1%			1.54 (1.42, 1.68)	<0.001	1.54 (1.41, 1.68)	<0.001
Using statins (yes vs. no)					0.76 (0.32, 1.80)	0.53
Serum HDL cholesterol						
Serum HDL cholesterol, per 10 mg/dL	0.96 (0.86, 1.07)	0.41	1.00 (0.89, 1.11)	0.94	0.99 (0.89, 1.11)	0.91
Glycosylated hemoglobin A1c, per 1%			1.55 (1.43, 1.68)	<0.001	1.55 (1.43, 1.68)	<0.001
Using statins (yes vs. no)					0.75 (0.32, 1.77)	0.51
Incident Macular Edema						
Serum total cholesterol						
Serum total cholesterol, per 20 mg/dL	1.08 (1.00, 1.17)	0.06	0.99 (0.91, 1.08)	0.81	0.99 (0.91, 1.08)	0.81
Glycosylated hemoglobin A1c, per 1%			1.46 (1.31, 1.63)	<0.001	1.46 (1.31, 1.63)	<0.001
Using statins (yes vs. no)					1.07 (0.41, 2.78)	0.89
Serum HDL cholesterol						
Serum HDL cholesterol, per 10 mg/dL	0.83 (0.71, 0.96)	0.01	0.87 (0.75, 1.00)	0.06	0.87 (0.75, 1.00)	0.06
Glycosylated hemoglobin A1c, per 1%			1.44 (1.30, 1.60)	<0.001	1.44 (1.29, 1.60)	<0.001
Using statins (yes vs. no)					1.01 (0.39, 2.62)	0.98

CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; PDR, proliferative diabetic retinopathy.

Duration of diabetes was used as the time scale.

Model 1 includes serum total cholesterol (for analyses of total cholesterol) or serum HDL cholesterol (for analyses of HDL cholesterol).

Model 2 includes all variables in Model 1 plus glycosylated hemoglobin A1c.

Model 3 includes all variables in Model 2 plus statin use.