Association of Serum Lipids With Macular Thickness and Volume in Type 2 Diabetes Without Diabetic Macular Edema

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Submitted: August 11, 2013
Accepted: February 11, 2014

Citation: Sasaki M, Kawashima M, Kawasaki R, et al. Association of serum lipids with macular thickness and volume in type 2 diabetes without diabetic macular edema. *Invest Ophthalmol Vis Sci*. 2014;55:1749–1753. DOI:10.1167/iovs.13-13035

Purpose. To assess the relationship between macular thickness and volume as characterized by optical coherence tomography (OCT) and known risk factors for diabetic retinopathy (DR) or macular edema (DME) in type 2 diabetic patients with no DME.

Methods. Seventy-four patients with type 2 diabetes without DME and no or only minimal DR ($n = 67$ with no DR; $n = 7$ with minimal DR; mean age, 59.5 years) were recruited at a tertiary eye hospital. Central subfield macular thickness (CSMT; circle of 500-μm radius) and central subfield macular volume (CSMV) were measured using spectral-domain OCT. Associations between OCT parameters and known risk factors for DR were examined using multiple linear regression models.

Results. The mean CSMT and CSMV values were 273.7 ± 17.8 μm and 0.215 ± 0.015 mm^3, respectively. After adjusting for age, sex, duration of diabetes, hemoglobin A1c, and urine protein, low-density lipoprotein (LDL) cholesterol was positively associated with CSMT and CSMV; each 1 mmol/L increase in LDL was associated with a mean increase in CSMT of 6.52 μm (95% confidence interval [CI], 1.96–11.08; $P = 0.006$) and a mean increase in CSMV of 0.0047 mm^3 (95% CI, 0.001–0.0085; $P = 0.015$).

Conclusions. A higher LDL cholesterol level was associated with increased CSMT and CSMV in diabetic patients without DME. Prospective longitudinal studies are warranted to assess whether having both elevated levels of LDL and higher CSMT or CSMV is a risk indicator for subsequent development of DME.

Keywords: macular edema, diabetes, optical coherence tomography, diabetic macular edema, macular thickness

With an increasing global prevalence of diabetes, diabetic retinopathy (DR) has become a leading cause of vision impairment. Advanced management of DR by pan-laser photocoagulation and pars plana vitrectomy enables us to prevent blindness from proliferative DR, whereas diabetic macular edema (DME) still remains a common cause of moderate to severe vision loss in patients with diabetes.[1–3] The Meta-Analysis for Eye Disease (META-EYE) Study Group provided data from 22,896 individuals with diabetes, 6.81% of whom had DME.[4] There are approximately 21 million people with DME worldwide.

Risk factors for the development and progression of DME have been investigated extensively and confirmed in multiple clinical studies.[5–13] Known risk factors include hemoglobin A1c (HbA1c), blood pressure, and serum lipids.[5–13] Most previous studies have focused on risk factors associated with clinically significant macular edema (CSME), the most severe form of DME defined by photo grading in the Early Treatment Diabetic Retinopathy Study (ETDRS).[14,15] However, associations of these risk factors with early retinal pathology in diabetes in the absence of DME have not been widely studied.[16,17]

Optical coherence tomography (OCT) has emerged as one of the main methods used to characterize the presence or severity of DME. Optical coherence tomography provides quantitative measures of DME and is particularly useful in clinical trials.[18–23] It is an objective and potentially more sensitive way to assess early retinal changes in diabetes such as macular thickness and volume in persons without DME.

In this study, we investigated the association between macular thickness and volume measured by OCT and known risk factors for DR or DME in patients with diabetes without DME.

Methods

Study Population

We recruited subjects with type 2 diabetes who were at least 20 years old and routinely followed at the general or

specialized internal medicine clinic and ophthalmology clinic of Keio University Hospital in Tokyo, Japan, from April 2011 to January 2012. Eligibility criteria included (1) absence of DME, defined as no retinal thickening of the macula based on clinical and OCT examination, and central subfield macular thickness (mean retinal thickness within the 1-mm-diameter circle) < 320 μm in men and <305 μm in women[24]; (2) no or minimal DR (ETDRS level 10: no retinopathy or level 20: microaneurysms only); (3) absence of high myopia, defined as a refractive error of less than –6 diopters; (4) no prior treatment for macular edema or DR; (5) no history of glaucoma and cup-to-disc ratio < 0.7; (6) no history of any retinal diseases; and (7) no history of major ocular surgery within 6 months.

We recruited 74 eligible participants (47 males and 27 females). All research and measurements adhered to the tenets of the Declaration of Helsinki and were approved by the Ethical Committee of Keio University School of Medicine. Each patient provided written informed consent after a detailed explanation of the nature and possible consequences of the study procedures.

Assessment of Macular Thickness and Volume

Spectral-domain OCT (SD-OCT) images were obtained with the Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany), using the automatic real-time eye tracker to eliminate motion artifacts. Following pupil dilatation, three to five high-resolution horizontal line scans (9 mm) and two or three high-density volume scans were obtained from the macular region. Based on the quality scores, a 19-mm horizontal foveal scan image and one volume scan image were chosen for analysis. Quality scores for scans were assigned by the Spectralis and expressed as a signal-to-noise ratio in decibels (dB). Scans above 20 dB were considered high quality. Two measurements were recorded: central subfield macular thickness (CSMT) and central subfield macular volume (CSMV), defined as the mean retinal thickness and the total volume within the central 1 mm surrounding the central circular zone, respectively. Measurements from right eyes were used for analysis.

Blood and Urine Chemistry

Blood samples were drawn in the morning after an overnight fast at routine medical follow-ups and tested with an automatic clinical chemistry analyzer (LABOSPECT 008; Hitachi, Tokyo, Japan). Serum levels of creatinine, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were measured using enzymatic methods.[25] Hemoglobin A1c was assessed using high-performance liquid chromatography and calculated. Proteinuria were measured by urine dipstick (Uriflet S; ARKRAY, Inc., Kyoto, Japan) and read by a technician 1 minute after dipping and assessed as none, trace, 1+, 2+, 3+, or 4+. None and trace were defined as negative and 1+ or greater as positive for proteinuria.

Assessment of Other Systemic Risk Factors

Each participant underwent a comprehensive assessment that included a range of clinical and anthropometric measurements collected. Key covariates included age, sex, duration of diabetes (years), diabetic medication use, use of antihypertensive medications, use of lipid-lowering medications, HbA1c level (percentage), blood pressure (mm Hg), body mass index, and smoking status.

Table 1. Baseline Characteristics and Macular Morphological Parameters

Characteristics, $n = 74$	Mean (±SD)/ Median (Interquartiles)
Age, y	59.5 (±8.0)
Sex, male, %	63.5
Refractive error, diopters	−1.5 (2.2)
Body mass index, kg/m^2	24.9 (±4.2)
Duration of diabetes, y	11.5 (±7.6)
Hemoglobin A1c	7.2 (±1.4)
Use of insulin, %	17.6
Use of antihypertension medication, %	45.9
Use of lipid-lowering medication, %	25.7
Systolic blood pressure, mm Hg	124.8 (±19.7)
Diastolic blood pressure, mm Hg	81.7 (±16.8)
Positive urine protein, %	14.9
Creatinine, μmol/L	66.3 (56.2–123.1)
Total cholesterol, mmol/L	5.1 (±1.0)
Triglycerides, mmol/L	1.5 (±1.4–1.9)
HDL cholesterol, mmol/L	1.4 (±0.5)
LDL cholesterol, mmol/L	2.9 (±0.9)
Macular morphological parameters	
Minimum thickness, μm	220.6 (±17.4)
Central subfield macular thickness, μm	273.7 (±17.8)
Central subfield macular volume, $\times 10^{-3}$ mm^3	214.9 (±14.5)
Total macular volume, mm^3	8.61 (±0.41)

Data are mean (±SD) for normally distributed data, or median (interquartile ranges) for skewed data unless otherwise stated.

Statistical Analysis

The associations of CSMT or CSMV and systemic characteristics including lipid levels were assessed using multiple linear regression models adjusted for age, sex, duration of diabetes, HbA1c, and urine protein. Association estimates (beta coefficients) from these models were expressed as mean difference in CSMT (μm) and CSMV (mm^3) per unit change in each potential associated risk factor. All P values reported were two tailed, and $P < 0.05$ was considered significant. Statistical analyses were performed using SPSS software version 19.0 (IBM Corporation, New York, NY).

Results

Characteristics and macular morphological parameters of the study sample are presented in Table 1. For the 74 patients (67 with no DR and 7 with minimal DR), the average CSMT was 273.7 ± 17.8 μm, and CSMV was 0.215 ± 0.015 mm^3. The minimum central subfield thickness (within the 1-mm-diameter circle) was 220.6 ± 17.4 μm, and mean total macular volume was 8.61 ± 0.410 mm^3.

Compared to male patients, female patients had less CSMT (–13.6 μm in mean CSMT; 95% confidence intervals [CI], –21.6, –5.57) and CSMV (–0.011 mm^3 in mean CSMV; 95% CI, –0.018, –0.005). In unadjusted analyses, total cholesterol and higher LDL cholesterol levels, higher HbA1c levels, and presence of urine protein were associated with greater CSMT (Table 2). Each 1 mmol/L increase in total cholesterol was associated with 4.81-μm greater CSMT (95% CI, 0.73, 8.89). Higher LDL cholesterol levels, higher HbA1c levels, and presence of urine protein were also associated with greater CSMV (Table 2, Fig.). Use of lipid-lowering medication was not associated with CSMT or CSMV (Table 2).

After adjusting for age, sex, duration of diabetes, HbA1c, and urine protein, LDL cholesterol levels were significantly

Table 2. Crude Associations Between Systemic Risk Factors and Macular Parameters

	Central Subfield Macular Thickness, μm		Central Subfield Macular Volume, $\times 10^{-3}$ mm^3	
Systematic Characteristics	**Mean Difference (95% CI)**	***P***	**Mean Difference (95% CI)**	***P***
Age, female vs. male	−13.6 (−21.6, −5.57)	0.001	−11.4 (−17.90, −4.80)	0.001
Age, per 1 y	−0.42 (−0.93, 0.01)	0.11	−0.32 (−0.74, 0.13)	0.14
Refractive error, per 1 diopter	0.27 (−1.66, 2.21)	0.78	−0.17 (−1.75, 1.41)	0.83
Body mass index, per 1 kg/m^2	−0.51 (−1.50, 0.49)	0.31	−0.47 (−1.28, 0.34)	0.26
Systolic blood pressure, per 1 mm Hg	−0.15 (−0.37, 0.06)	0.15	−0.14 (−0.31, 0.03)	0.106
Diastolic blood pressure, per 1 mm Hg	0.18 (−0.07, 0.44)	0.15	0.17 (−0.03, 0.38)	0.11
Creatinine, per 1 μmol/L	0.012 (−0.019, 0.042)	0.45	0.0076 (−0.017, 0.032)	0.54
Urine protein, positive vs. negative	12.3 (0.90, 23.7)	0.035	9.12 (−0.26, 18.5)	0.056
Total cholesterol, per 1 mmol/L	4.81 (0.73, 8.89)	0.021	3.68 (0.34, 7.03)	0.031
LDL cholesterol, per 1 mmol/L	6.45 (1.67, 11.24)	0.009	4.76 (0.82, 8.71)	0.019
HDL cholesterol, per 1 mmol/L	−4.82 (−14.15, 4.50)	0.31	−3.10 (−10.77, 4.56)	0.32
Triglycerides, per 1 mmol/L	1.62 (−2.35, 5.60)	0.42	1.28 (−1.97, 4.53)	0.43
Duration of diabetes, per 1 y	0.18 (−0.37, 0.72)	0.52	0.17 (−0.28, 0.62)	0.45
Hemoglobin A1c, per 1%	4.23 (1.23, 7.23)	0.006	3.58 (1.13, 6.02)	0.005
Use of lipid-lowering medication, yes vs. no	2.87 (−5.56, 11.31)	0.50	2.40 (−4.49, 9.29)	0.49

associated with CSMT and CSMV; each 1 mmol/L increase in LDL cholesterol was associated with a 6.52-μm greater CSMT (95% CI, 1.96, 11.08) and 0.0047 mm^3 greater CSMV (95% CI, 0001, 0.0085), respectively (Table 3). Total cholesterol, HDL cholesterol, and triglycerides were not significantly associated with CSMT and CSMV after adjustment for these covariables (Table 3).

We analyzed data from a small sample of normal (nondiabetic) controls to clarify if similar lipid–retinal thickness association presents in subjects without diabetes, and found no similar association in 25 normal subjects (data not shown).

Discussion

In this study, we demonstrated positive, linear associations between LDL cholesterol level and macular thickness and volume in 74 patients with type 2 diabetes without DME.

Previous studies have found that serum lipids were associated with macular hard exudates, CSME, and DME.[4,13,16,26–29] The ETDRS reported an association of total and LDL cholesterol levels with the presence of hard exudates in the macula in patients with DR.[26] Idiculla et al.[27] reported that cholesterol levels were associated with hard exudates in center of the macula, and LDL cholesterol levels were associated with CSME in patients with type 2 diabetes. The Chennai Urban Rural Epidemiology Study (CURES) Eye Study also found a correlation between LDL cholesterol level and CSME and DME.[12] The Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study[13] reported that total cholesterol related to CSME and that LDL cholesterol and non-HDL cholesterol related to DME. Our results are consistent with findings from these studies.

However, Benarous et al.[16] found no associations between serum lipids and DR, DME, and macular thickness or volume, measured using time-domain OCT (TD-OCT) in patients with various stages of DR, while they found a significant association with CSME. In the study by Benarous et al.,[16] TD-OCT was used, whereas in our study SD-OCT was used. The greater resolution obtained using SD-OCT may possibly make it more sensitive in capturing subtle changes than TD-OCT, thus leading to the difference in findings. Moreover, the homoge-

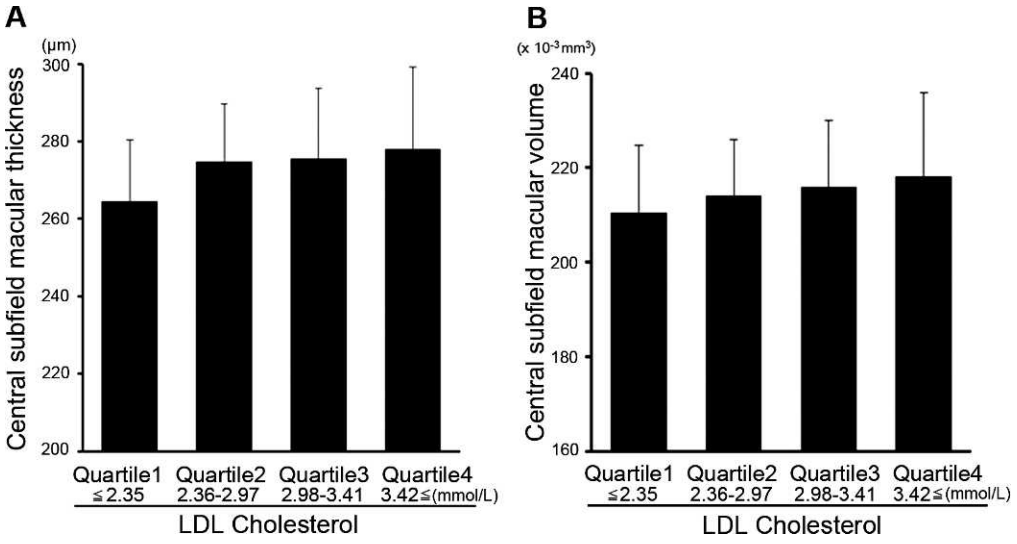

Figure. Associations between OCT parameters and serum LDL cholesterol. (**A**) Central subfield macular thickness by quartiles of LDL cholesterol. (**B**) Central subfield macular volume by quartiles of LDL cholesterol.

Table 3. Associations Between Serum Lipids and Central Macular Parameters After Adjustment for Age, Sex, Hemoglobin A1c, and Urine Protein

	Central Subfield Macular Thickness, μm		Central Subfield Macular Volume, × 10^{-3} mm^3	
Serum Lipids, per 1 mmol/L	**Mean Difference (95% CI)**	***P***	**Mean Difference (95% CI)**	***P***
Total cholesterol	3.13 (−1.07, 7.32)	0.14	2.34 (−1.09, 5.76)	0.18
LDL cholesterol	6.52 (1.96, 11.08)	0.006	4.70 (0.95, 8.45)	0.015
HDL cholesterol	−3.43 (−12.00, 5.14)	0.43	−1.63 (−8.67, 5.40)	0.64
Triglycerides	−1.79 (−5.68, 2.09)	0.36	−1.50 (−4.67, 1.67)	0.35

neous nature of our sample in terms of DR levels may have been favorable for detecting an association.

There is a possibility that lipid-lowering medications could modify the association between serum lipid and DME or macular morphology. Fenofibrate, a lipid-lowering agent that acts mostly on triglycerides, may slow the development and progression of DR and DME,[30] although its effects on DR in those trials were independent of lipid levels.[30] Statins have been shown to have retinal vascular effects[31,32]; however, they did not affect DR severity according to findings from a few studies.[33,34] We included the use of lipid-lowering medication in the multivariable-adjusted regression model and found that the association between LDL levels and CSMT and CSMV remained significant (data not shown).

There has been evidence suggesting a link between thicker central macula and the incidence of DME.[17,35] A recent Diabetic Retinopathy Clinical Research Network (DRCR.net) study reported that 38% of persons with no DME and a center point thickness in a relatively high range progressed to having DME over 2 years.[35] One retrospective study reported a 15% increased risk of DME for each 10-μm increase in CSMT in patients with type 2 diabetes.[17] According to these study findings, a thicker CSMT in patients with diabetes may be a sign of early alteration leading to clinical DME. Central subfield macular thickness could therefore be a useful marker to guide clinical practice in patients with diabetes.

We adopted the criterion for abnormal retinal thickness from the DRCR.net study, which is CSMT values $>$ 2 standard deviations above the average CSMT found in diabetic patients with minimal or no DR.[24,36] It should be noted that eyes with normal retinal thickness does not mean that they have normal retinal function. Dhamdhere et al.[37] reported that neuroretinal function measured by multifocal electroretinography was not associated with retinal thickness in the corresponding retinal area measured by OCT in patients with diabetes but no retinopathy. Functional changes caused by early diabetes could precede structural changes including retinal thickness.

Our study describes a well-characterized clinical sample of diabetic patients, and we used good-quality images by SD-OCT with an eye tracking function captured by trained examiners. We also recognize several limitations with our study. First, the study's cross-sectional nature does not allow us to assess the temporal sequence of these associations, and the sample size was relatively small. Therefore, future longitudinal studies with larger sample size are warranted. Second, we have analyzed data from a small sample of normal (nondiabetic) controls. Although no similar association was found in the 25 normal subjects for whom we have relevant data, confirmation from future studies is needed.

In conclusion, in this sample of type 2 diabetic patients without DME, we found that a higher level of LDL cholesterol was associated with increased CSMT and CSMV. Our findings suggest that the associations between elevated levels of LDL and CSMT or CSMV are observed even before the development of DME, and may indicate a clinical or metabolic transition stage to clinical manifestation of DME. Prospective studies are warranted to assess whether diabetic patients with elevated levels of LDL and thicker CSMT or greater CSMV are at higher risk of developing DME, as well as whether interventions to lower LDL levels reduce the risk of development of DME at an early stage.

Acknowledgments

We thank Jonathan E. Noonan and Yoji Takano for advice on manuscript preparation; Misa Suzuki for data collection; and Miho Kawai, Yuta Shigeno, other orthoptists, and medical staff from our clinic for their technical assistance.

Disclosure: **M. Sasaki**, None; **M. Kawashima**, None; **R. Kawasaki**, None; **A. Uchida**, None; **T. Koto**, None; **H. Shinoda**, None; **K. Tsubota**, None; **J.J. Wang**, None; **Y. Ozawa**, None

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