AMERICAN ACADEMY™
OF OPHTHALMOLOGY

Diabetic Retinopathy in Patients with Dyslipidemia: Development and Progression

Chi-Juei Jeng, MD,[1,2,3] *Yi-Ting Hsieh, MD, PhD,*[3] *Chung-May Yang, MD,*[3] *Chang-Hao Yang, MD, PhD,*[3] *Cheng-Li Lin, MS,*[4] *I-Jong Wang, MD, PhD*[3,5]

Purpose: To investigate the association of dyslipidemia with the development of diabetic retinopathy (DR).
Design: A prospective cohort from the Longitudinal Health Insurance Database in Taiwan.
Participants: Patients with diabetes mellitus (DM) aged ≥18 years from this cohort.
Methods: A logistic regression model considering age, sex, and adapted Diabetes Complication Severity Index (aDCSI) including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy cardiovascular disease, cerebrovascular disease, peripheral arteriolar disease, and metabolic disease. We estimated the propensity score for disease assignment probability for each included patient with DM and dyslipidemia. For each patient, a comparison patient without dyslipidemia was matched with a propensity score using a greedy algorithm. The standardized mean differences method was used to measure the difference in means or proportions divided by the pooled standard deviation of a variable. We calculated the incidence densities of nonproliferative DR (NPDR), diabetic macular edema (DME), and proliferative DR (PDR) as total events divided by the sum of follow-up duration, and the incidence curves were measured using the Kaplan−Meier method. The log-rank test was applied to test the differences of incidence curves.
Main Outcome Measures: Hazard ratios (HRs) for DR.
Results: Our results demonstrated that the cumulative incidence of NPDR, DME, and PDR significantly increased in patients with DM and dyslipidemia compared with those without before adjustment for covariates ($P < 0.001$). Adjusted HRs for NPDR, DME, and PDR in patients with dyslipidemia were 1.77 (95% confidence interval [CI] = 1.63−1.92), 2.34 (95% CI = 1.24−4.41), and 1.07 (95% CI = 0.91−1.27), respectively. The risks of NPDR, DME, and PDR increased in patients who had underlying complications according to the aDCSI. Only statin use had a protective effect against the development of NPDR (HR = 0.83; 95% CI = 0.76−0.90), but it had no effect on DME and PDR. The protective effect was not significantly different between patients with and without dyslipidemia.
Conclusion: Dyslipidemia is involved in the development of DR at an earlier stage, but the role of lipid-modulating agents in DR requires additional study. *Ophthalmology Retina 2017;■:1−8 © 2017 by the American Academy of Ophthalmology*

Supplemental material is available at www.ophthalmologyretina.org.

Diabetic retinopathy (DR), a debilitating microvascular complication of diabetes mellitus (DM), leads to visual impairment in adults.[1] The results of epidemiological studies conducted on patients with type 1 or 2 DM in the Diabetes Control and Complications Trial and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study have revealed the importance of glycemic control in delaying or preventing DR development.[2−4] Moreover, disease duration; elevated blood pressure, lipid profile, and serum advanced glycation end product (AGE) levels; evidence of early-stage atherosclerosis; increased caliber of retinal blood vessels; and several genetic factors (e.g., those related to enzymes involved in glucose and lipid metabolism) also contribute to DR development.[2,5,6] Among these, dyslipidemia is considered a major risk factor for cardiovascular and ocular complications in individuals with DM.[7−12]

In general, dyslipidemia is a modifiable and independent risk factor for macro- and microvascular diseases, and its treatment might aid in preventing diabetic complications.[13−15] In type 2 DM, altered lipid metabolism precedes glucose elevation,[14] and dyslipidemia further contributes to diabetic neuropathy development in individuals with type 2 DM.[14−16] By contrast, lipid profiles are always normal in patients with type 1 DM at the time of diabetes diagnosis, but dyslipidemia may develop later in the course of type 1 DM.[17] Abnormal lipid profiles coincide with the delayed onset and progression of diabetic neuropathy, as seen in type 2 DM.[18] The association of hyperlipidemia and dyslipidemia with DR has been investigated extensively.[19−21] According to the results of the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), total cholesterol and low-density lipoprotein cholesterol (LDL-C) are associated with the presence of hard exudates in patients with DR.[19] Also, according to the Early Treatment Diabetic Retinopathy Study (ETDRS), lipid lowering may also decrease the risk of hard-exudate

http://dx.doi.org/10.1016/j.oret.2017.05.010
ISSN 2468-6530/17

formation and associated vision loss in patients with DR.[22,23] Besides the ETDRS[22,23] and the WESDR,[19] the Hoorn study[24] and the Atherosclerosis Risk in Communities study[25] identify the profile characteristics of patients with DM for treating diabetic dyslipidemia, particularly for patients who may possibly develop DR. Regarding other biomarkers, the severity of DR is inversely associated with apolipoprotein (Apo) A1 but positively associated with ApoB and the ApoB-to-ApoA1 ratio.[20,21] Because LDL-C levels do not reflect the classic diabetic dyslipidemia of hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C) levels, the definite association among the development of vision-threatening DR, proliferative DR (PDR), and diabetic macular edema (DME) in patients with DM and dyslipidemia remains elusive.[26] Although measurements of plasma ApoB100 and non−HDL-C levels add no new lipid biomarkers that may improve the definition of dyslipidemia,[27,28] the role of lipid biomarkers still requires clarification in light of the persistent failure of epidemiological studies to demonstrate a clear association between traditional lipids and DR.[29] Moreover, statins, nicotinic acid, and fibrates are current treatment approaches for dyslipidemia[30] and can more favorably control DR.[7] However, vision-threatening complications still develop even after correcting conventional abnormal lipid profiles,[31] because lipoprotein can extravasate through retinal capillaries, leading to DME.[32,33] Therefore, the effect of lipid-modifying drugs on DR development warrants further elucidation and investigation. We conducted this nationwide cohort study by recruiting patients with type 2 DM so that we could investigate the correlation between dyslipidemia, lipid-modifying drugs, and DR occurrence and progression.

Methods

Data source

The Taiwan government has established a single-payer compulsory health insurance program, National Health Insurance (NHI), for 23 million Taiwan citizens and residents. All NHI claims data are collated in the NHI Research Database (NHIRD). This study collected the claims data from a subset of the NHIRD, the Longitudinal Health Insurance Database (LHID), which contains the claims data of 1 million NHI insurants. According to a Taiwan government report, insurant age and sex do not differ between the LHID and NHIRD. The LHID includes several files, such as the registry files, disease record files (registered per International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]), prescription files, and medical expenditure files of beneficiaries. The Taiwan government releases these data set after a deidentification process.

This study was approved by the ethics review board of China Medical University (CMUH104-REC2-115).

Study population

Patients with DM (ICD-9-CM code 250) and aged ≥18 years were randomly selected from the LHID, and 2 cohorts were created: dyslipidemia and nondyslipidemia. In both cohorts, we excluded patients with a history of nonproliferative DR (NPDR), DME, or PDR before the index date. If the eligible patients with diabetes had also been prescribed a medication with Anatomical Therapeutic Chemical code C10 (lipid-modifying agents) for disease treatment for either outpatient or inpatient care in the index year, they were considered to have a diagnosis of dyslipidemia.[34−36] Medication exposure was determined from both inpatient and outpatient prescriptions. To standardize the dosage of drugs across multiple types, the defined daily dose (DDD) was used. The DDD is a validated unit of drug consumption that is defined by the World Health Organization as "the assumed average maintenance dose per day for a drug used for its main indication in adults."[37] The cumulative DDD represented the total dose of each drug prescribed during the study period. In our cohort, statin or fibrate users were characterized by statin or fibrate use of ≥28 cumulative DDDs in 1 year. The dyslipidemia cohort comprised patients with DM who had been diagnosed as having dyslipidemia (ICD-9-CM code 272); the index date for dyslipidemia was set at the date of initial dyslipidemia diagnosis during 2000 to 2010. Our comparison cohort, the nondyslipidemia cohort, comprised patients with DM and without dyslipidemia matched (1:1) by propensity score. Through propensity scores, we estimated the probability of disease assignment for each study participant using a logistic regression model that considered age, sex, the adapted Diabetes Complication Severity Index (aDCSI), and comorbidities (diabetic nephropathy, diabetic nephropathy, hypertension, heart disease, cerebrovascular disease, or peripheral arteriolar disease); for each case, we matched a control through propensity-score matching using a greedy algorithm.[38−42]

The outcomes of interest in this study were diagnoses of (1) NPDR (ICD-9-CM codes 250.5, 362.01, 362.03−06 362.1, 362.81, 362.82), (2) PDR (ICD-9-CM codes 362.02, 379.23) confirmed with administration of panretinal photocoagulation treatment, and (3) DME (ICD-9-CM codes 362.53, 362.83, 362.07) and treatment with intravitreal injections. The diagnosis of DME and the administration of intravitreal injection treatment rely on the results of optical computed tomography or fluorescein angiography, as requested by insurance claimants to the NHI program for reimbursement. Each patient included in this study was followed for each outcome. The diagnosis of NPDR, PDR, or DME was confirmed if the same diagnosis was noted for 2 subsequent visits. Patients with NPDR were followed until they withdrew from the NHI program, PDR or DME events occurred, or they reached the end of the 5-year follow-up period. Furthermore, we followed each patient independently for different outcomes. The follow-up terminated when a patient discontinued NHI, when PDR or DME events occurred, or on December 31, 2013. The secondary outcome was the 5-year risk of PDR and DME after NPDR occurred.

We considered the effects of aDCSI, comorbidity, and dyslipidemia medication. The aDCSI assesses DM severity in 7 dimensions: retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic.[43] We categorized aDCSI scores as 0, 1, 2, and ≥3. Furthermore, we considered the following comorbidities: hypertension (ICD-9-CM codes 401−405), heart disease (ICD-9-CM codes 410−429), cerebrovascular disease (ICD codes 430−438), and peripheral arteriolar disease (ICD-9-CM codes 440−448). The dyslipidemia medications included statins and fibrates.

Statistical analysis

We analyzed our cohorts, and we represent our data as means and corresponding standard deviations for continuous variables and as number and percentage for categorical variables (e.g., sex, comorbidity, medication). To assess structural differences between the dyslipidemia and nondyslipidemia cohorts, we used the standardized mean differences method and measured a difference in