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ORIGINAL ARTICLE

Factors associated with non-proliferative diabetic retinopathy in patients with type 1 and type 2 diabetes: the Japan Diabetes Complication and its Prevention prospective study (JDCP study 4)

Ryo Kawasaki[1,2] · Shigehiko Kitano[3] · Yukihiro Sato[4] · Hidetoshi Yamashita[5] · Rimei Nishimura[6] · Naoko Tajima[6] · For the Japan Diabetes Complication and its Prevention prospective (JDCP) study Diabetic Retinopathy working group

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Abstract

Aims This study aims to identify associations of non-proliferative diabetic retinopathy (NPDR) in the Japan Diabetes Complication and its Prevention prospective (JDCP) study, a nation-wide study capturing real-world practice for diabetes in Japan.

Methods We recruited patients with type 1 and type 2 diabetes mellitus aged between 40 and 75 years from 464 hospitals and clinics. Seven thousand and seven hundred patients fulfilled the inclusion criteria, and 5852 patients were included for this specific analysis. Multiple logistic regression models were used to identify associated factors of NPDR.

Results Of the 363 patients with type 1 diabetes, 83 patients (22.8%) had NPDR; there were significant associations of duration of diabetes and high-density lipoprotein cholesterol with the presence of NPDR. Of the 5489 patients with type 2 diabetes, 1515 (27.6%) had NPDR. Female, duration of diabetes, lifetime maximum body weight, treatment types, systolic blood pressure, and the number of oral hypoglycemic agents (OHA) and antihypertensive drug were associated with increased odds of having NPDR. Diastolic BP, body mass index, alcohol intake, and the number of lipid-lowering drugs were associated with lower odds of having NPDR. Statin and fibrate use was associated with lower odds of having NPDR; this association was confirmed in the model adjusting for the propensity score for taking fibrate or statin (odds ratio 0.80, 95% confidence interval 0.70–0.92; $p = 0.002$).

Conclusions There was a potential protective association of lipid-lowering medication (statin or fibrate) and statin use and the presence of NPDR in patients with type 2 diabetes in the JDCP study.

Keywords Diabetic retinopathy · Type 1 diabetes · Type 2 diabetes · Risk factor · Epidemiology

Introduction

Diabetic retinopathy is a common microvascular complication of both type 1 and type 2 diabetes, affecting one-third of the patients with diabetes [1]. Although there has been

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✉ Ryo Kawasaki
ryo.kawasaki@ophthal.med.osaka-u.ac.jp

[1] Department of Vision Informatics (Topcon), Osaka University Graduate School of Medicine, 2-2 Yamada-Oka, Suita-city, Osaka, Japan

[2] Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

[3] Diabetes Center, Tokyo Women's Medical University, Tokyo, Japan

[4] Jichi Medical University, Shimotsuke, Tochigi, Japan

[5] Department of Ophthalmology, Yamagata University Faculty of Medicine, Yamagata, Japan

[6] Division of Diabetes, Metabolism and Endocrinology Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan

accumulated evidence that the prevalence [1] and incidence rates [2] of diabetic retinopathy is declining among patients with diabetes, its burden is still high given the number of people with diabetes is still increasing [3].

Treatment modalities for vision-threatening diabetic retinopathy, namely proliferative diabetic retinopathy and diabetic macular edema, have been dramatically advanced with laser treatment, vitreous surgery, and most recently anti-vascular endothelial growth factor (VEGF) intravitreal injections [4–6]. However, the importance of detecting diabetic retinopathy at an early stage has not faded, because understanding the risk associations of developing diabetic retinopathy has a potential to mitigate the burden caused by diabetic retinopathy through interventions to the modifiable risk factors.

The position statement by the American Diabetes Association [7] has described systemic associations of diabetic retinopathy such as hyperglycemia, nephropathy, hypertension, and dyslipidemia. Regarding dyslipidemia, two randomized clinical trials, the Action to Control Cardiovascular Risk in Diabetes study (ACCORD) study and the Fenofibrate Intervention and Event Lowering in Diabetes Study (FIELDS study) [8–10], demonstrated the beneficial effect of fenofibrate intake in reducing the risk of progression to advanced microvascular diabetic complications, including diabetic retinopathy needing a laser treatment. Interestingly, those studies [8–10] reported a protective effect of fenofibrate intake avoiding treatments such as laser retinal photocoagulation for diabetic retinopathy independent of lipid levels. Little is known, however, whether taking statin or fibrate reduces the risk of developing diabetic retinopathy, especially in real-world practice.

The Japan Diabetes Complication and its Prevention prospective (JDCP) study is a multi-center observational study led by the Japan Diabetes Society [11]. This study aims to capture day to day practice at diabetes clinics all over Japan to illustrate the characteristics and associations of diabetes and its risk factors. This specific report is a part of the JDCP study describing the cross-sectional baseline characteristics regarding the early stage of diabetic retinopathy in the JDCP study. It aims to identify potential risk associations modifiable by intervention to reduce the risk of diabetic retinopathy based on real-world clinical data in Japan.

Methods

Subjects

The JDCP Study was initiated in 2007, collecting information on patients with type 1 and type 2 diabetes mellitus, aged between 40 and 75 years from university hospitals, secondary or tertiary hospitals, and clinics where diabetologists reside (total 464 clinics) [11]. Seven thousand and seven hundred patients who fulfilled the inclusion criteria were pre-registered between June 2007 and November 2009. Patients who have the following conditions were excluded:

1. not able to attend the clinic regularly,
2. on dialysis,
3. have proliferative diabetic retinopathy,
4. have been diagnosed with malignancy within 5 years, or
5. determined by study physician to be not appropriate for this study.

There were 6338 patients remaining. Of them, 5852 had detailed information on the severity of diabetic retinopathy and were included in this analysis. All the data were collected with pre-defined forms from all the clinics and hospitals. Information collected in this study included background characteristics, anthropometry, blood tests, kidney function, electrocardiograms, fundus findings, neuropathy parameters, periodontitis, and treatment for diabetes.

Definition of diabetic retinopathy

In this study, patients with proliferative diabetic retinopathy were removed by one of the exclusion criteria (3) above; therefore, our study is for non-proliferative diabetic retinopathy (NPDR). Definitions of NPDR were adopted from the international clinical diabetic retinopathy severity scale [12] as below:

1. Mild NPDR—micro-aneurysms only.
2. Moderate NPDR—more than mild, but less than severe NPDR.
3. Severe NPDR—one of the signs below without signs of proliferative diabetic retinopathy:
   (a) more than 20 intra-retinal hemorrhages in all 4 quadrants,
   (b) definite venous beadings in more than or equal to 2 quadrants,
   (c) definite intra-retinal microvascular abnormality at least in 1 quadrant.

Persons with retinal neovascularization, vitreous hemorrhages, or pre-retinal hemorrhages were excluded because of having proliferative diabetic retinopathy.

Statistical analysis

Background characteristics between patients with or without NPDR were compared with Pearson's Chi squared test, Student's *t* test, or Wilcoxon rank-sum test depending on the

types of data. A p value of < 0.05 was considered as statistically significant.

Multiple logistic regression models were used to identify the associated factors of NPDR. Adjusted odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. For patients with type 1 diabetes, we included age (years old), gender (male/female), hemoglobin A1c (HbA1c) (%), duration of diabetes (years), insulin units used, body mass index (BMI) (kg/m^2), systolic blood pressure (BP) (mmHg), high-density lipoprotein (HDL) cholesterol (mg/dl), non-HDL cholesterol (mg/dl), low-density lipoprotein (LDL) cholesterol (mg/dl), alcohol intake, smoking, estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2), number of oral hypoglycemic agents (OHA), number of antihypertensive agents, and number of lipid-lowering agents as covariates. To avoid biased estimation due to the small number of patients with type 1 diabetes, we used a penalized maximum likelihood estimation proposed by Firth. For patients with type 2 diabetes, calculation was based on age, gender, HbA1c, duration of diabetes, medication types, BMI, lifetime maximum body weight, systolic BP, diastolic BP, non-HDL cholesterol, HDL cholesterol, LDL cholesterol, eGFR, history of myocardial infarction, history of stroke, alcohol intake, smoking, number of OHA, and number of antihypertensive agents as covariates. The number of drugs was then replaced with the individual drug in the alternative models as a sensitivity analysis.

Associations of lipid-lowering agents and NPDR in persons with type 2 diabetes were examined with a propensity score adjusted model [13]. We first estimated the propensity score using a lipid-lowering agent as an outcome with the multiple logistic regression model including 19 covariates. The odds ratio for the presence of NPDR between patients with or without lipid-lowering agents was calculated after adjusting for the propensity score as a covariate. A p value of < 0.05 was considered as statistically significant in this analysis. All analyses were performed using Stata MP (Version 15.1, College Station, TX, USA).

Results

The background characteristics of patients included in this study stratified by types of diabetes are shown in Supplemental Table. The mean age was 61.1 years and 58.7% were male. The median duration of diabetes was 9.0 years (the inter-quartile range 5.0–15.0 years) and mean hemoglobin A1c was 57.0 mmol/l (7.4%).

Type 1 diabetes

Of the 363 patients with type 1 diabetes, 83 (22.8%) had NPDR. The severity of DR for patients with type 1 diabetes, was 85.5 and 14.5% for mild to moderate NPDR and severe NPDR, respectively. Compared to patients without NPDR, patients with NPDR were significantly older, had a longer duration of diabetes, larger BMI, higher systolic blood pressure, higher creatinine, lower estimated glomerular filtration rate (eGFR), and had been using more insulin (Table 1).

A multiple logistic regression model using the presence of NPDR as an outcome and gender, age, hemoglobin A1c, duration of diabetes, insulin units used, BMI, systolic blood pressure, non-HDL cholesterol, LDL cholesterol, alcohol intake, smoking (current or past smoker vs. never smoked), eGFR, and the number of oral hypoglycemic agents, antihypertensive agents, and lipid-lowering agents as covariates was used. There were significant associations of longer duration of diabetes with increasing odds of having NPDR, and higher HDL cholesterol with reduced odds of having NPDR (Table 2).

Type 2 diabetes

Of the 5489 patients with type 2 diabetes, 1515 (27.6%) had NPDR. The severity of DR in patients with type 2 diabetes was 79.5 and 20.5% for mild to moderate NPDR and severe NPDR, respectively. Comparing patients with and without NPDR, patients with NPDR were older, had a longer duration of diabetes, less body weight, higher systolic blood pressure, higher random glucose, higher hemoglobin A1c, higher creatinine, lower eGFR, female gender, taking insulin, using more insulin units, performing self-measurement of blood glucose level (SMBG), and more likely to take alcohol (Table 3).

In multiple logistic regression analysis, female gender, duration of diabetes, lifetime maximum body weight, systolic blood pressure, number of OHA, and number of antihypertension drugs were associated with increased odds of having NPDR (Table 4). Insulin treatment with or without OHA was associated with increased odds of having NPDR when compared with those with diet therapy alone [adjusted OR for insulin use: 4.51 (95% CI 3.14–6.48) $p < 0.001$; adjusted OR for insulin plus OHA: 3.76 (95% CI 2.57–5.50), $p < 0.001$] (Table 4). On the contrary, diastolic blood pressure, body mass index, alcohol intake, and the number of lipid-lowering drugs were associated with lower odds of having NPDR (Table 4). An alternative model replacing the number of lipid-lowering drugs with individual lipid-lowering drug class of statin and fenofibrate was constructed. There remained significant associations of statin use (0.79, 95% CI 0.68–0.92; $p = 0.002$). Although a point estimate of adjusted OR for fibrate intake remained in protective direction, its 95% CI was wide and did not reach statistical significance (0.76, 95% CI 0.56–1.06; $p = 0.105$) (Table 5).

We additionally examined a model adjusting for the propensity score for taking fibrate and/or statin. A balancing

Table 1 Background characteristics of patients with type 1 diabetes by presence of non-proliferative diabetic retinopathy

	NPDR absent ($N=280$)	NPDR present ($N=83$)	p value
Age, years	55.6	58.9	0.004
Duration of diabetes, years*	7 (4–13)	18 (11–25)	< 0.001
Body weight, kg	56.2	58.2	0.114
Lifetime maximum body weight, kg	62.0	63.6	0.207
Age at lifetime maximum body weight, years	42.0	41.4	0.701
Body height, cm	160.0	159.8	0.810
BMI, kg/m^2	21.9	22.7	0.025
Waist circumference, cm	77.7	79.7	0.109
Systolic blood pressure, mmHg	123.1	131.2	< 0.001
Diastolic blood pressure, mmHg	72.0	72.0	0.969
Fasting glucose, mg/dl	141.2	114.5	0.093
Random glucose, mg/dl	173.6	179.6	0.614
HbA1c, mmol/l [%]	62.0 [7.8]	62.0 [7.8]	0.934
Total cholesterol, mg/dl	198.2	196.7	0.680
LDL cholesterol, mg/dl	106.9	107.3	0.886
HDL cholesterol, mg/dl	73.3	69.9	0.137
Triglycerides, mg/dl*	74 (56.5–91.5)	70 (54–102)	0.531
Non-HDL cholesterol, mg/dl	125.2	125.7	0.869
Creatinine, mg/dl	0.68	0.73	0.026
eGFR, mL/min/1.73 m^2	82.4	76.5	0.006
Insulin dose used, unit	31.6	37.4	0.010
Gender			
Men (%)	43.2	44.6	0.826
Treatment			
Diet treatment only	–	–	0.469
OHA only	1.1	0.0	
Insulin only	83.6	88.0	
OHA + insulin	15.4	12.0	
Insulin use			
Yes	98.9	100.0	0.344
Self-measurement of blood glucose level			
Yes	92.1	95.2	0.299
Alcohol intake			
Yes	26.8	21.7	0.548
Current or past smoking			
Yes	38.2	42.2	0.142

NPDR non-proliferative diabetic retinopathy, *OHA* oral hypoglycemic agents, *BMI* body mass index, *HbA1c* hemoglobin A1c, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *eGFR* estimated glomerular filtration rate

*Median (inter-quartile range)

plot of the propensity score between those who were using lipid-lowering agents and those who were not is shown in Supplemental Figure S1. We first examined the validity of the propensity score by comparing the distribution in each of the covariates before and after propensity score adjustment and confirmed that there were no statistically significant differences between the two groups. Mean and median bias was decreased from 14.3 and 13.5 to 2.4 and 2.1%, respectively. The variance ratio proposed by Rubin [14] was also decreased from 1.25 to 0.79, which is considered to be within the acceptable range of 0.5–2.0. We used this propensity score as a covariate to adjust the association between lipid-lowering medication use and the presence of NPDR. In persons with type 2 diabetes mellitus, there were 1989 persons using statins only and 269 persons using fibrates only. There were 33 persons who used both statins and fibrates. A significant association was observed between those who took fibrate or statin and those who did not take

Table 2 Multiple logistic regression for the prevalence of non-proliferative diabetic retinopathy in patients with type 1 diabetes

Fully adjusted model	Adjusted OR (95% CI)	*p* value
Women (vs. men)	1.41 (0.62, 3.18)	0.409
Age (per + 1 year)	1.01 (0.96, 1.05)	0.759
HbA1c (per + 11 mmol/l or + 1%)	1.15 (0.89, 1.48)	0.293
Duration of diabetes (per + 1 year)	1.11 (1.07, 1.16)	< 0.001
Insulin units used (per + 1 unit)	1.02 (0.99, 1.04)	0.198
BMI (per + 1 kg/m^2)	1.03 (0.89, 1.19)	0.672
Systolic blood pressure (per + 1 mmHg)	1.02 (1.00, 1.05)	0.071
Non-HDL cholesterol (per + 1 mg/dl)	0.99 (0.96, 1.02)	0.553
HDL cholesterol (per + 1 mg/dl)	0.98 (0.96, 1.00)	0.041
LDL cholesterol (per + 1 mg/dl)	1.01 (0.98, 1.05)	0.518
Alcohol intake (yes vs. no)	0.87 (0.37, 2.08)	0.759
Current or past smoking (yes vs. no)	1.90 (0.94, 3.83)	0.074
eGFR (per + 1 mL/min/1.73 m^2)	0.99 (0.97, 1.01)	0.311
Number of OHA (per + 1 agent)	0.48 (0.18, 1.26)	0.136
Number of antihypertensive agents (per + 1 agent)	1.33 (0.87, 2.03)	0.183
Number of lipid-lowering agents (per + 1 agent)	1.76 (0.82, 3.74)	0.144

OHA oral hypoglycemic agents, *BMI* body mass index, *HDL* high-density lipoprotein, *OR* odds ratio, *CI* confidence interval

fibrate or statin (propensity score adjusted OR 0.80, 95% CI 0.70–0.92; $p=0.002$). Taking statin alone was significantly associated with lower odds of having NPDR (propensity score adjusted OR 0.85, 95% CI 0.74–0.98; $p=0.024$). Persons taking fibrate alone were also marginally associated with lower odds of having NPDR (propensity score adjusted OR 0.75, 95% CI 0.55–1.03; $p=0.072$). Although persons taking both fibrate and statin seemed to be less likely to have NPDR based on the point estimate (propensity score adjusted OR 0.65), this did not reach statistical significance (Table 6). There was no suggestion of interaction between taking fibrate and statin ($p=0.960$; data not shown). In persons with type 1 diabetes mellitus, there were 84 persons using statins only and only 3 persons using fibrate only; there were none using both statins and fibrates. Therefore, we did not perform a similar analysis for persons with type 1 diabetes mellitus.

Discussion

In this JDCP study baseline survey, the prevalence of non-proliferative diabetic retinopathy in patients with type 1 diabetes and type 2 diabetes was 22.8 and 27.6%, respectively. The prevalence of diabetic retinopathy in patients with type 2 diabetes was similar to that reported in the Japan Diabetes Complications Study (JDCS) [15]. At the baseline of JDCS, the proportion of patients with type 2 diabetes who had mild NPDR was 25.1% with a mean duration of diabetes of 12.8 years. Our observation in this study was slightly higher compared to the prevalence of diabetic retinopathy reported in the meta-analysis based on 35 epidemiological studies [1], where age-standardized prevalence of any diabetic retinopathy for patients with type 2 diabetes in studies completed in the era of 2000s was 24.79% (24.57–25.00%); the prevalence of NPDR which was estimated excluding PDR (prevalence 3.47%) was 21.32%. All of these prevalence data were mostly from hospital-based studies including the current study. Therefore, this may overestimate the number of patients with DR compared to the general diabetic population.

In this study, we found that the duration of diabetes and systolic blood pressure factors showed consistent associations with NPDR in both patients with type 1 or type 2 diabetes. The importance of managing hypertension in preventing diabetic retinopathy has been confirmed in multiple studies and a systematic review [16] and our study supports this current understanding. An unexpected non-significant association with HbA1c and the prevalence of NPDR was surprising. Although HbA1c was associated with the presence of NPDR in patients with type 2 diabetes before adjustment, there was no significant association after adjusting for other covariates. We speculate that this is because more than 90% of the patients recruited into this study were already treated with OHA and/or insulin. Also, patients recruited into this study had a relatively good glucose control at baseline [Hb A1c for type 1 diabetes 62.0 mmol/l (7.8%) and for type 2 diabetes 57.0 mmol/l (7.4%)]. Given the cross-sectional nature of this study, confirmation of association between glucose control and diabetic retinopathy needs further observation in longitudinal follow-up.

Table 3 Background characteristics of patients with type 2 diabetes based on the presence of non-proliferative diabetic retinopathy

	NPDR absent ($N=3974$)	NPDR present ($N=1515$)	p value
Age, years old	61.1	62.1	< 0.001
Duration of diabetes, years [median (inter-quartile range)]	8 (4–13)	13 (8–19)	< 0.001
Body weight, kg	64.2	63.1	0.003
Lifetime maximum body weight, kg	70.8	71.0	0.636
Age at lifetime maximum body weight, years old	48.1	45.0	< 0.001
Body height, cm	161.6	160.4	< 0.001
BMI, kg/m^2	24.5	24.5	0.506
Waist circumference, cm	86.4	86.5	0.707
Systolic blood pressure, mmHg	128.6	132.5	< 0.001
Diastolic blood pressure, mmHg	74.7	74.5	0.433
Fasting glucose, mg/dl	135.4	137.8	0.208
Random glucose, mg/dl	159.7	166.2	0.001
Insulin Resistance Index	7.7	8.1	0.671
HbA1c, mmol/l (%)	57.0 (7.4)	60.0 (7.6)	< 0.001
Total cholesterol, mg/dl	195.4	193.5	0.052
LDL cholesterol, mg/dl	113.2	111.8	0.110
HDL cholesterol, mg/dl	57.6	57.2	0.382
Triglycerides, mg/dl [median (inter-quartile range)]	108 (77–152)	104 (77–150)	0.282
Non-HDL cholesterol, mg/dl	137.9	136.3	0.108
Creatinine, mg/dl	0.75	0.78	0.003
eGFR, mL/min/1.73 m^2	77.7	76.0	0.004
Insulin dose used, unit	25.1	27.7	0.001
Gender			
Men (%)	61.0	56.3	0.001
Treatment			
Diet treatment only	12.7	3.3	< 0.001
OHA only	65.8	53.0	
Insulin only	10.9	19.7	
OHA + insulin	10.4	23.9	
Insulin use			
Yes	21.3	43.6	< 0.001
Self-measurement of blood glucose level			
Yes	23.8	41.3	< 0.001
Alcohol intake			
Yes	40.6	33.9	< 0.001
Current or past smoking			
Yes	37.6	38.3	0.770

NPDR non-proliferative diabetic retinopathy, *OHA* oral hypoglycemic agents, *BMI* body mass index, *HbA1c* hemoglobin A1c, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *eGFR* estimated glomerular filtration rate

We did not find an association between smoking habits and increased prevalence of NPDR in patients with type 1 diabetes. Association between smoking and risk of diabetic retinopathy has been inconsistent and controversial [17]. A cohort study in Denmark reported that smoking was not associated with PDR, while there was a suggestion of association with increased prevalence of NPDR [18], which was consistent with our finding. We need to examine if smoking is associated with increased risk of incidence or progression of diabetic retinopathy in the longitudinal follow-up study which is ongoing. Given that more than 30% of the study participants were smokers in this study, an intervention of smoking cessation might impact on reducing the risk of diabetic retinopathy.

The current medication and the number of drugs were associated with the presence of NPDR in persons with type 2 diabetes. Interestingly, the number of drugs lowering glucose and blood pressure was associated with increased odds

Table 4 Multiple logistic regression for the prevalence of non-proliferative diabetic retinopathy in patients with type 2 diabetes

Model 1	Adjusted OR (95% CI)	*p* value
Women (vs. men)	1.45 (1.21, 1.74)	< 0.001
Age (per + 1 year)	0.99 (0.98, 1.00)	0.250
HbA1c (per + 11 mmol/l or + 1%)	1.02 (0.97, 1.09)	0.437
Duration of diabetes (per + 1 year)	1.05 (1.04, 1.06)	< 0.001
Treatment		
Diet treatment only	1	
OHA only	1.47 (1.01, 2.14)	0.042
Insulin only	4.51 (3.14, 6.48)	< 0.001
HA + insulin	3.76 (2.57, 5.50)	< 0.001
BMI (per + 1 kg/m^2)	0.94 (0.92, 0.97)	< 0.001
Lifetime maximum body weight (per + 1 kg)	1.02 (1.01, 1.02)	< 0.001
Systolic blood pressure (per + 1 mmHg)	1.02 (1.02, 1.03)	< 0.001
Diastolic blood pressure (per + 1 mmHg)	0.99 (0.98, 1.00)	0.010
Non-HDL cholesterol (per + 1 mg/dl)	1.00 (1.00, 1.00)	0.774
HDL cholesterol (per + 1 mg/dl)	1.00 (0.99, 1.00)	0.058
LDL cholesterol (per + 1 mg/dl)	1.00 (0.99, 1.00)	0.567
eGFR (per + 1 mL/min/1.73 m^2)	1.00 (1.00, 1.00)	0.976
Alcohol intake (yes vs. no)	0.81 (0.69, 0.95)	0.009
Current or past smoking (yes vs. no)	1.01 (0.88, 1.16)	0.886
Past history of myocardial infarction (yes vs. no)	0.96 (0.66, 1.40)	0.829
Past history of stroke (yes vs. no)	0.80 (0.57, 1.11)	0.179
Number of OHA (per + 1 agent)	1.30 (1.18, 1.43)	< 0.001
Number of antihypertensive agents (per + 1 agent)	1.17 (1.09, 1.26)	< 0.001
Number of lipid-lowering agents (per + 1 agent)	0.80 (0.69, 0.92)	0.002

OHA oral hypoglycemic agents, *BMI* body mass index, *HDL* high-density lipoprotein, *OR* odds ratio, *CI* confidence interval

Table 5 Sensitivity analysis replacing the number of drugs with specific agents in the multiple logistic regression for the prevalence of non-proliferative diabetic retinopathy in patients with type 2 diabetes

	Model 2		Model 3		Model 4	
	Adjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Sulfonylureas	1.84 (1.50, 2.24)	< 0.001	–		–	
Biguanides	1.33 (1.13, 1.56)	< 0.001	–		–	
α-Glucosidase inhibitors	1.15 (0.98, 1.34)	0.091	–		–	
Glinides	1.25 (0.94, 1.66)	0.128	–		–	
Thiazolidinediones	1.12 (0.93, 1.34)	0.234				
Angiotensin receptor blockers	–		1.21 (1.03, 1.41)	0.021	–	
Angiotensin converting enzyme inhibitors	–		0.99 (0.77, 1.28)	0.950	–	
Ca blockers	–		1.30 (1.10, 1.54)	0.002	–	
Statin	–		–		0.79 (0.68, 0.92)	0.002
Fibrate	–		–		0.76 (0.56, 1.06)	0.105

Adjusted for other covariates in Model 1

OR odds ratio, *CI* confidence interval

of having NPDR, while the number of drugs lowering lipids was negatively associated with NPDR. This observation was confirmed by alternative analysis using the propensity score for adjustment. Although the odds ratios estimated in the model with the propensity score adjustment were attenuated compared to logistic regression analysis, it remained significant. Given the cross-sectional nature of this analysis, the logic behind this observation needs to be speculated.

Table 6 Propensity score adjusted odds ratio for non-proliferative diabetic retinopathy in patients with type 2 diabetes

	Adjusted OR (95% CI)	*p* value
NO fibrate or statin	1	
Fibrate or statin	0.80 (0.70, 0.92)	0.002
Statin alone	0.85 (0.74, 0.98)	0.024
Fibrate alone	0.75 (0.55, 1.03)	0.072
Fibrate and statin	0.65 (0.24, 1.78)	0.406

Adjusted using the propensity score as a covariate. The propensity score for lipid-lowering medication use was calculated based on age, sex, hemoglobin A1c, duration of diabetes, medication, body mass index, lifetime maximum body weight, systolic blood pressure, diastolic blood pressure, non-high-density lipoprotein cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein, estimated glomerular filtration ratio, history of myocardial infarction, history of stroke, alcohol intake, smoking, number of oral hypoglycemic agents, and number of antihypertensive agents

The number of medications for lowering glucose and blood pressure naturally reflects that the baseline glucose level and blood pressure level were high, and this was associated with increased risk of having NPDR in this analysis. However, an inverse association with the number of lipid-lowering medications does not hold the same logic, because there was little association between high cholesterol or triglycerides level and the prevalence of NPDR. Therefore, it might be natural to hypothesize that lipid-lowering medication of statin and fibrate might have beneficial influence in reducing the development of NPDR. We consider that fibrate use did not reach a significant association, due to the fact that the number of patients who were under fibrate was smaller than the number of patients who were under statins. The point estimate of odds ratio for fibrate use was smaller than that for statin use, suggesting that fibrate use might have a larger impact on NDPR consistently in our models if more patients take fibrate.

A detailed mechanism of why lipid-lowering medication use decreases the risk of DR has not been fully understood. There has been a link between hyperlipidemia and increased risk of diabetic retinopathy and especially with hard exudates [19]. Sasaki et al. [20]. also demonstrated that higher LDL cholesterol level was associated with increased macular thickness, a sign of diabetic macular edema. Moreover, recent findings from clinical trials revealed that statin plus fibrate or fibrate alone reduced the risk of clinical outcomes related to diabetic retinopathy and diabetic macular edema. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD)-EYE study [8], fenofibrate plus simvastatin compared with placebo plus simvastatin was associated with decreased risk of progression of diabetic retinopathy or induction of laser treatment. In the FIELD Study, fenofibrate 200 mg/day intake was associated with approximately 30% risk reduction for having pan-retinal photocoagulation in diabetic retinopathy [9, 10]. The risk of the composite outcome of progression of diabetic retinopathy, incidence of diabetic macular edema, and laser treatment were also decreased by 34% compared to the placebo-treated group. A 30% reduction of laser photocoagulation in diabetic retinopathy and diabetic macular edema by taking fenofibrate, independent of blood glucose level, blood pressure level, and even lipid level, might provide supportive evidence to consider fenofibrate with or without statins as a candidate to be used in the management of diabetic retinopathy. Our study findings support this by showing that those who take statin or fibrate are at lower odds of having NPDR in a real-world clinical setting. To date, there has been no clear evidence supporting that lipid-lowering medication or statin or fibrate reduces the risk of developing DR. We consider our findings to be supportive of the hypothesis that these medications might be beneficial in lowering the risk of development of DR, in addition to lowering the risk of progression of DR.

We must acknowledge that this current analysis is a cross-sectional study and it does not fully support the effectiveness of statin and fibrate in a longitudinal study. We need to confirm our findings with ongoing longitudinal follow-up study. It should also be noted that those with a severe stage of diabetic retinopathy have been excluded at recruitment. Adherence to the standard and regular monitoring for glucose, blood pressure, and lipid concentrations might be influenced by the effect of unmeasured characteristics such as lifestyle and socioeconomic status or education status in the association between medication use and risk of microvascular complications including DR. This might also be applicable to alcohol intake and smoking habit.

In conclusion, we reported the baseline characteristics of the JDCP study participants stratified by type of diabetes. We described associated factors for both patients with type 1 diabetes and type 2 diabetes, with a contrast in associations between the types of diabetes. We also report a potential association of lipid-lowering medication use (fibrate or statin use) on decreased odds of having NPDR, which was also confirmed by a propensity score adjustment. Further longitudinal analysis will elucidate if those characteristics observed in this cross-sectional analysis are associated with a progression and incidence of the advanced stage of diabetic retinopathy.

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Compliance with ethical standards

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study. The study protocol was reviewed and approved by the Research Ethics Review Board of the Japan Diabetes Society (approved on July 2, 2013; study title "Japan Diabetes Complication and its Prevention Prospective study (JDCP study); approval number: not applicable).

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