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Original Article

Risk factors associated with diabetic retinopathy onset and progression in diabetes patients: a Taiwanese cohort study

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Abstract: Diabetic retinopathy (DR) is a common complication of type 2 diabetes mellitus (T2DM) and the leading cause of adult blindness. This study aimed to clarify the risk factors associated with DR onset and progression in patients with T2DM in Taiwan. This retrospective analysis enrolled 743 T2DM patients, including 170 with DR and 573 without DR at baseline who were enrolled in the Diabetes Shared-Care Program. The average follow-up period was 2.9 years. Variables, including demographic characteristics, DM duration, anthropometric data and clinical laboratory results, were compared between patients with DR at baseline, those with new-onset DR, and patients without DR using a chi-squared test and one-way ANOVA. A multivariate Cox proportional hazards model was performed to identify risk factors associated with progression of preexisting DR or new-onset DR. During the follow-up period, 38 (22.4%) patients with preexisting DR experienced disease progression, and 91 (15.9%) patients had new-onset DR. Multivariate analysis revealed that the presence of neuropathy (HR: 3.96, 95% CI: 1.84, 8.53) and diastolic blood pressure (HR: 1.05, 95% CI: 1.02, 1.08) were associated with increased risk of DR progression (both $P < 0.001$). Factors associated with new-onset DR included neuropathy, systolic BP, cholesterol, and updated mean of HbA1c (all $P \leq 0.001$). The risk factors associated with DR onset and progression in Taiwanese patients with T2DM are different. Neuropathy and blood pressure increased the risk of both DR onset and progression; however, the risk of DR onset was also increased with updated mean of HbA1c and cholesterol.

Keywords: Complications, diabetes mellitus, diabetic retinopathy, glycated hemoglobin, risk factor

Introduction

Diabetic retinopathy (DR) is a common microvascular complication of diabetes mellitus (DM) and the leading cause of visual impairment in adults. DR is also associated with increased risk of complications, such as stroke and cardiovascular events [1]. The incidence of DR increases with diabetes duration, increasing linearly after 10 years, and it is detected in one-third of all patients with DM for 25 years [2]. While almost all patients with type 1 diabetes (T1DM) will eventually develop DR, > 60% of patients with type 2 diabetes (T2DM) will also experience DR [3]. Worldwide prevalence of DR was estimated to be 4% in 1995 and is expected to increase to 5.4% by 2025 [4]. A study of Chinese diabetic and pre-diabetic patients (i.e., with impaired glucose regulation) revealed that DR prevalence was 9.4% among the diabetic patients and 2.5% among those with pre-diabetes [5]. In Taiwan, the prevalence of DR was 6% in 2000 and 8.91% in 2009, demonstrating an increasing trend, which was noted especially in middle-aged (40-65 y) and older (> 65 y) adults [6]. This was corroborated by results of a large, longitudinal study, which revealed that progressive DR among diabetic patients enrolled in Taiwan's National Health Insurance program was directly associated with increasing healthcare costs.

DR develops as a result of uncontrolled glycemia that produces multiple characteristic features of DR, including microaneurysms, vitreous hemorrhage, retinal hemorrhages, cotton-

wool spots and hard exudates [7]. DR progression begins with mild non-proliferative abnormalities that are characterized by increasing vascular permeability, which evolves into moderate and severe non-proliferative DR with vascular closure and finally proliferative DR with new retinal blood vessel growth on the retina and vitreous surface [3]. Retinal thickening from leaky blood vessels leads to macular edema, which can develop at any stage of DR. These progressive changes may be accelerated by poor glycemic control and hypertension, which have been identified as risk factors for DR progression [8]. In addition, changes in metabolic control and systolic blood pressure are risk factors for progression to photocoagulation for diabetic macular edema [9]. However, the strongest predictor for DR onset and progression may be the duration of diabetes, which was demonstrated in the Wisconsin Epidemiologic Study of Diabetic Retinopathy [8] through increased prevalence (from 8% at 3 y to 60% at 10 y and 80% at 15 y) and increased incidence (4-y incidence increased from 0% in first 5 y to 28% in 13-14 y of diabetes).

The incidence of DR has been described in previous studies along with risk factors associated with DR in certain populations [8, 9]. Intervention studies have assessed microvascular complications of DR, but improved glucose control has tended to limit the onset and progression of DR and other complications in patients with T1DM and T2DM [10], which may account somewhat for lack of agreement on long-term risk factors for DR. Although the prevalence of DR is known to be increasing in Taiwan [6], and studies of DR prevalence have also identified risk factors [11], few studies have investigated the predictors of DR onset or progression in Taiwanese T2DM patients. Through the Diabetes Shared-Care Program, the Department of Health in Taiwan has promoted the diabetes care network throughout the country, relying on the cooperation of medical professionals in various organizations to provide examinations, inspections, health education and complete patient tracking to help reduce the incidence or delay diabetes complications. This study took advantage of the defined population of T2DM patients in the Diabetes Shared-Care Program and aimed to clarify the risk factors associated with DR onset and progression in these patients. The results of this study may help to encourage the active screening and identification of patients at risk of developing DR and promote the timely control of this critical complication of diabetes.

Materials and methods

Subjects

A total of 743 patients previously diagnosed and treated for T2DM were recruited from the Diabetes Shared Care Program in our institution between March 2002 and March 2014 were included in this retrospective cohort study. The inclusion criteria were as follows: adult T2DM patients enrolled in the Diabetes Shared-Care Program with a diabetes diagnosis confirmed twice in three months by the same certified physician. There were no exclusion criteria. Baseline and follow-up data included retinal examinations and biochemical tests at baseline through the follow-up period, which was conducted every three months. Since patients had joined the care network at different times, the follow-up periods varied in length among the patients, and the average follow-up for all enrolled subjects was 2.9 y. Among the 743 patients, 170 subjects had been previously diagnosed with DR (DR group) while the remaining 573 subjects were without DR (non-DR group) at baseline. Data from two sub-cohorts, including 38 subjects with progression of pre-existing DR and 91 patients who were without DR at baseline but developed new-onset DR within the follow-up period were also analyzed. The Internal Review Board of Kuang Tien General Hospital reviewed and approved the study protocol. Patient data included in analysis did not include patient identification; therefore, signed informed consent was waived for this study.

Definitions

T2DM was diagnosed (1) based on the American Diabetes Association criteria [12] (HbA1c $\geq$ 6.5% [13]) or (2) use of any antidiabetic agents (oral or injection) for more than 2 months. Patients were followed-up regularly as outpatients. As part of the follow-up care, a retinal examination was performed by an eye specialist by direct ophthalmoscopy or indirect ophthalmoscopy following mydriasis. DR was diagnosed according to ICD-9-CM codes, and severity was determined using fluorescein angio-

grams as previously described [14]. DR progression was diagnosed on the basis of results from a funduscopic examination by an ophthalmology specialist and was classified as deteriorating/progressing retinopathy from non-proliferative to pre-proliferative or proliferative, and with and without macular edema. Non-proliferative DR was diagnosed by the presence of retinal microaneurysm, hemorrhage, soft exudate, venous beading, and intraretinal microvascular abnormalities. Pre-proliferative DR was diagnosed upon identification of new vessels in the retina without meeting the definition of proliferative DR, which was diagnosed based on neovascularization at the disk (NVD) or elsewhere (NVE). HbA1c variability was determined using three models. Model 1 considered the influence of updated mean A1c results from 6 months onward on the risk of subsequent microvascular complications. Model 2 included variability of A1c expressed as intrapersonal SDs of mean HbA1c serial values throughout the follow-up periods for individual patients. Because the number of visits per patient would differ and cause the SD appear to be greater among those with more visits, it was adjusted by dividing the SD value by [n/(n_1)]. Model 3 applied χ^2 tests to compare proportions and used t tests to compare variables between normoalbuminuria and microalbuinuria. Cox regression analysis was used to determine whether HbA1 variability was an independent predictor.

Main outcome measures

Demographic characteristics, DM duration and anthropometric measures, including body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and body weight, were collected for all patients. Laboratory examinations at baseline and during follow-up included baseline and follow-up values for fasting plasma glucose (FPG), cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL), serum glutamic-pyruvic transaminase (SGPT), urine microalbumin/creatinine ratio (UACR), creatinine, and HbA1c. Smoking status and alcohol consumption were also recorded. Clinical characteristics/medical history included previously diagnosed hypertension, cardiovascular disease, foot deformity, nephropathy, neuropathy and stroke.

Statistical analysis

Continuous variables are presented as mean and standard deviation (mean ± SD). Categorical variables are presented as count and percentage. Differences between groups of DR at baseline, DR onset during follow-up period, and without DR were compared using one-way ANOVA test for continuous variables and Chi-square test or Fisher's exact test with Yate's correction if any cell number was < 5 or close to zero for categorical variables. A univariate Cox proportional hazards model was used to evaluate correlations between patients' variables and progression of preexisting DR or new-onset DR events. A multivariate Cox proportional hazards model was performed to identify risk factors associated with progression of preexisting DR or new-onset DR events; the independent variables with $P < 0.05$ in the univariate Cox model were included in the multivariate Cox proportional hazards model according to forward conditional selection. Since some variables, including age, duration of DM, BMI, SBP, DBP, fasting plasma glucose (FPG), cholesterol, triglyceride, low-density lipoprotein cholesterol (LDLc), high-density lipoprotein cholesterol (HDLc), glutamic-pyruvic transaminase (GPT), urine microalbumin/creatinine ratio (UACR), creatinine, and glycated hemoglobin HbA1c, may change over time, a Cox model with time-dependent covariate was used in the univariate and multivariate analyses. The results of the Cox regression model were summarized by hazard ratio (HR) with 95% CI. Data were analyzed using SPSS 18.0 statistics software (SPSS Inc, Chicago, IL, USA). All statistical assessments were two-sided and evaluated at the 0.05 level of significant difference.

Results

Subjects' demographic and clinical characteristics

A total of 743 patients with T2DM were included in this study, and their baseline characteristics are summarized in **Table 1**. The average follow-up period of all subjects was 2.9 years, and the total follow-up time was 2,171 person-years. As shown in **Table 1**, 170 subjects were diagnosed with pre-existing DR (pre-existing DR group), 91 patients had new-onset DR within the follow-up period (new-onset DR group), and 482 subjects had no observed DR during the study period (non-DR group). Significant dif-

Table 1. Patients' demographic and clinical characteristics at baseline (n = 743)

Variables	Pre-existing DR (n = 170)	New-onset DR (n = 91)	Non-DR (n = 482)	*P* value
Age (y)[1]	61.1 ± 9.4	62.0 ± 12.1	57.5 ± 13.3†,‡	< 0.001*
Gender, male[2]	75 (44.1)	44 (48.4)	310 (64.3)	< 0.001*
Education[2]				< 0.001*
Illiteracy/Literacy	57 (35.4)	26 (29.9)	89 (19.4)	
Elementary school	73 (45.3)	41 (47.1)	173 (37.8)	
High school	23 (14.3)	14 (16.1)	135 (29.5)	
College/University or above	8 (5.0)	6 (6.9)	61 (13.3)	
DM duration (y)[1]	16.3 ± 6.9	14.8 ± 7.7	9.9 ± 6.2†,‡	< 0.001*
BMI[1]	25.8 ± 3.9	26.0 ± 3.8	26.1 ± 3.9	0.570
Systolic BP (mmHg)[1]	136.9 ± 17.6	134.2 ± 18.3	129.9 ± 15.7†	< 0.001*
Diastolic BP (mmHg)[1]	77.5 ± 9.7	76.3 ± 11.6	77.5 ± 10.1	0.581
FPG (mg/dL)[1]	176.8 ± 49.0	153.9 ± 45.6†	154.3 ± 48.5†	< 0.001*
Cholesterol (mg/dL)[1]	191.5 ± 51.0	176.1 ± 60.1	172.4 ± 55.9†	< 0.001*
Triglycerides (mg/dL)[1]	157.9 ± 96.9	166.4 ± 147.0	148.5 ± 134.6	0.405
LDL (mg/dL)[1]	114.3 ± 34.9	109.4 ± 27.5	106.9 ± 31.7†	0.036*
HDL (mg/dL)[1]	43.4 ± 13.9	41.9 ± 13.1	43.6 ± 13.2	0.545
GPT (u/L)[1]	29.2 ± 18.2	32.9 ± 18.9	34.4 ± 23.8†	0.031*
UACR (mg/g)[1]	15.0 ± 72.3	2.0 ± 9.5	3.9 ± 27.3†	0.007*
Creatinine (mg/dL)[1]	1.02 ± 0.42	1.03 ± 0.32	0.94 ± 0.38†	0.011*
HbA1c (%)[1,3]	8.7 ± 1.6 (72 ± 18)	8.3 ± 1.8 (67 ± 19)	7.8 ± 1.6† (62 ± 18)	< 0.001*
Smoking status[2]				0.269
Never smoked	131 (78.4)	68 (76.4)	334 (70.2)	
Current smoker	27 (16.2)	16 (18.0)	102 (21.4)	
Former smoker	9 (5.4)	5 (5.6)	40 (8.4)	
Drinking[2]	13 (8.0)	8 (9.1)	35 (7.5)	0.876
Hypertension[2]	111 (65.3)	63 (69.2)	154 (32.0)	< 0.001*
Cardiovascular disease[2]	15 (8.8)	7 (7.7)	28 (5.8)	0.373
Foot deformity[2]	8 (4.7)	2 (2.2)	5 (1.0)	0.014*
Nephropathy[2]	66 (38.8)	32 (35.2)	73 (15.1)	< 0.001*
Neuropathy[2]	38 (22.4)	11 (12.1)	22 (4.6)	< 0.001*
Stroke[2]	8 (4.7)	2 (2.2)	12 (2.5)	0.307

Data are presented as [1]mean ± SD or [2]n (%). *P*-values are based on [1]one-way ANOVA test and Bonfferroni post-hoc comparisons; [2]Chi-square test. **P*<0.05 indicates a significantly difference among the three groups. †Indicates a significant difference as compared to those with DR at baseline. ‡Indicates a significant difference as compared to those with DR onset during follow-up period. Abbreviation: DR, diabetic retinopathy; DM, diabetic mellitus; BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SGPT, serum glutamic-pyruvic transaminase; UACR, urine microalbumin/creatinine ratio; HbA1c, glycated hemoglobin A1c; NS, non significant; SD, standard deviation. [3]HbA1c was listed by NGSP units (%).

ferences were shown among the three groups in age ($P < 0.001$), gender ($P < 0.001$), education level ($P < 0.001$), duration of DM ($P < 0.001$), SBP level ($P < 0.001$), FPG level ($P < 0.001$), cholesterol level ($P < 0.001$), LDL level ($P = 0.036$), GPT level ($P = 0.031$), UACR ($P = 0.007$), creatinine level ($P = 0.011$), HbA1c level ($P < 0.001$), hypertension ($P < 0.001$), foot deformity ($P = 0.014$), nephropathy ($P < 0.001$), and neuropathy ($P < 0.001$). Subjects in the two DR groups were significantly older and had longer DM duration than those in the non-DR group. In addition, patients with pre-existing DR had significantly lower GPT and significantly higher SBP, FPG, cholesterol, LDL, UACR, creatinine, HbA1c than the non-DR group (**Table 1**).

Clinical characteristics associated with DR progression

Among 170 subjects with evidence of DR at baseline, 38 subjects experienced DR progres-

Table 2. Unadjusted hazard ratios for clinical characteristics associated with progression of preexisting DR (n = 170) and new-onset DR for those without DR at baseline (n = 573)

	Progression (n = 170)		Onset of DR (n = 573)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Time-independent covariate				
Gender, male	1.14 (0.60, 2.19)	0.687	0.69 (0.46, 1.04)	0.080
Education				
Illiteracy/Literacy	reference		reference	
Elementary school	0.79 (0.38, 1.65)	0.536	0.92 (0.56, 1.51)	0.742
High school	0.62 (0.20, 1.88)	0.398	0.36 (0.19, 0.69)	0.002*
College/University or above	0.57 (0.07, 4.43)	0.594	0.33 (0.13, 0.79)	0.013*
Smoking status				
Never smoked	reference		reference	
Current smoker	2.30 (1.02, 5.22)	0.046*	0.81 (0.47, 1.40)	0.454
Former smoker	2.54 (0.59, 10.98)	0.211	1.15 (0.46, 2.85)	0.772
Drinking	2.51 (0.86, 7.30)	0.092	1.28 (0.62, 2.64)	0.511
Hypertension	0.86 (0.42, 1.73)	0.662	2.21 (1.41, 3.46)	0.001*
Cardiovascular disease	1.39 (0.43, 4.53)	0.586	1.49 (0.69, 3.21)	0.317
Foot deformity	0.55 (0.13, 2.27)	0.404	3.00 (0.74, 12.20)	0.126
Nephropathy	0.85 (0.45, 1.63)	0.627	1.57 (1.02, 2.42)	0.041*
Neuropathy	3.02 (1.56, 5.87)	0.001*	3.76 (2.00, 7.06)	< 0.001*
Stroke	1.99 (0.27, 14.87)	0.504	1.19 (0.28, 4.99)	0.817
Time-dependent covariate				
Age (y)	1.02 (0.98, 1.05)	0.379	1.03 (1.01, 1.05)	0.002*
DM duration (y)	0.95 (0.90, 0.996)	0.034*	1.02 (0.99, 1.06)	0.154
BMI	0.98 (0.90, 1.06)	0.583	1.01 (0.95, 1.07)	0.841
Systolic BP (mmHg)	1.02 (1.00, 1.04)	0.078	1.02 (1.01, 1.04)	0.001*
Diastolic BP (mmHg)	1.04 (1.01, 1.07)	0.005*	1.00 (0.98, 1.02)	0.810
FPG (mg/dL)	1.00 (0.99, 1.01)	0.722	1.00 (1.00, 1.01)	0.137
Cholesterol (mg/dL)	1.01 (1.00, 1.01)	0.058	1.01 (1.003, 1.014)	0.003*
Triglycerides (mg/dL)	1.00 (1.00, 1.01)	0.150	1.00 (1.00, 1.01)	0.308
LDL (mg/dL)	1.01 (1.00, 1.02)	0.162	1.00 (1.00, 1.01)	0.760
HDL (mg/dL)	0.99 (0.97, 1.02)	0.521	1.00 (0.99, 1.02)	0.650
SGPT (u/L)	1.01 (0.98, 1.03)	0.630	0.99 (0.98, 1.01)	0.385
UACR (mg/g)	1.00 (1.00, 1.00)	0.755	1.00 (1.00, 1.00)	0.899
Creatinine (mg/dL)	1.00 (0.89, 1.11)	0.947	1.04 (0.89, 1.23)	0.624
Updated mean of HbA1c (%)	0.95 (0.77, 1.18)	0.672	1.24 (1.06, 1.44)	0.007*
HbA1c (%)	0.95 (0.76, 1.19)	0.672	1.08 (0.95, 1.23)	0.252

*P < 0.05 indicates a significant difference. Abbreviation: DR, diabetic retinopathy; DM, diabetic mellitus; BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; SGPT, serum glutamic-pyruvic transaminase; UACR, urine microalbumin/creatinine ratio; HbA1c, glycated hemoglobin A1c; HR, hazard ratio; CI, confidence interval.

sion, 132 patients had stable disease, and 16 patients had regression during the study period. The cases of regression included seven with regression of pre-proliferative/proliferative disease to non-proliferative disease and nine with macular edema regression. Because the objective of this part of the study was to investigate the possible risk factors associated with deterioration, all 16 patients who had regression were classified as having no deterioration in the analysis. Univariate analysis showed that the time-independent covariates significantly associated with the progression of preexisting DR were current smoking status (P = 0.046) and neuropathy (P = 0.001); the time-dependent covariates associated with DR progres-

Table 3. Adjusted hazard ratios for clinical characteristics associated with progression of preexisting DR (n = 170) and new-onset DR for those without DR at baseline (n = 573)

	Progression (n = 170)		Onset of DR (n = 573)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Time-independent covariate				
Neuropathy	3.96 (1.84, 8.53)	< 0.001	4.87 (2.29, 10.35)	< 0.001
Time-dependent covariate				
Systolic BP (mmHg)			1.03 (1.01, 1.04)	0.001
Diastolic BP (mmHg)	1.05 (1.02, 1.08)	< 0.001		
Cholesterol (mg/dl)			1.01 (1.004, 1.02)	0.001
Updated mean of HbA1c (%)			1.42 (1.18, 1.72)	< 0.001

Abbreviation: DR, diabetic retinopathy; BP, blood pressure; HR, hazard ratio; CI, confidence interval.

sion were DM duration ($P = 0.034$) and DBP ($P = 0.005$; **Table 2**). Multivariate analysis revealed that only neuropathy and diastolic BP were associated with progression of preexisting DR (both $P < 0.001$), with a 3.96-fold increased risk as compared to those without neuropathy and a 1.05-fold higher risk of progression when diastolic BP increased by 1 mmHg (**Table 3**).

Clinical characteristics associated with new-onset DR

Among the 573 non-DR subjects at baseline, 91 had new-onset DR in the follow-up period. Univariate analysis showed that the time-independent covariates significantly associated with new-onset DR were high school education level ($P = 0.002$), college/university or above education level ($P = 0.013$), hypertension ($P = 0.001$), nephropathy ($P = 0.041$), and neuropathy ($P < 0.001$; **Table 2**). The time-dependent covariates associated with new-onset DR were age ($P = 0.002$), SBP ($P = 0.001$), cholesterol ($P = 0.003$), and updated mean of HbA1c ($P = 0.007$). As shown in **Table 3**, multivariate analysis revealed that new-onset DR was associated with neuropathy (HR: 4.87, 95% CI: 2.29, 10.35; $P < 0.001$), SBP (HR: 1.03, 95% CI: 1.01, 1.04; $P = 0.001$), cholesterol (HR: 1.01, 95% CI: 1.004, 1.02; $P = 0.001$), and updated mean of HbA1c (HR: 1.42, 95% CI: 1.18, 1.72; $P < 0.001$).

Discussion

Analysis of all the patients, including those without DR and patients with pre-existing DR and new-onset DR, showed differences between the DR and non-DR groups in gender, age, DM duration, hypertension, diabetic nephropathy and neuropathy, SBP, FPG and SGPT levels. The Cox regression analysis revealed that the presence of neuropathy and higher diastolic BP increased the risk of DR progression. Furthermore, multivariate analysis showed that neuropathy and blood pressure increased the risk of both DR onset and progression; however, the risk of DR onset was also increased with updated mean of HbA1c and cholesterol. Thus, the risk factors associated with DR onset and progression were different.

The main risk factors identified in the present study, namely duration of DM, hypertension, and neuropathy, are similar to those identified in other studies. In another study conducted in a Chinese population with in pre-diabetes and impaired glucose regulation, hypertension and obesity were the main risk factors for DR [5]. An updated report of the Wisconsin Epidemiologic Study of Diabetic Retinopathy [8] found that the predominant risk factors for proliferative DR were duration of diabetes and glycemic control, and that risk may be further increased by uncontrolled hypertension and male gender. Results from a longitudinal cohort study conducted across almost two decades indicated that blood pressure and fasting plasma glucose had long-term effects, both prospective and cumulative, on retinopathy and retinal vascular caliber [15]. The authors suggest that the effects of hypertension may be long-term markers of changes in the retinal microvasculature and thus predictive of retinopathy. We also noted in our study that the presence of neuropathology is predictive of DR, which may be due to a common etiology. Similarly, Nwanyanwu et al. [16] reported that, along with glycemic control, non-ophthalmologic manifestations of DM,

such as nephropathy and non-healing ulcers, were associated with the progression of non-proliferative DR to proliferative DR [16]. That type of progression-non-proliferative to proliferative DR-was shown to be associated with increases in health expenditures equivalent to over $3000 USD.

Regarding sex and DR risk, there is a lack of consistent results. The landmark Wisconsin Epidemiologic Study of Diabetic Retinopathy reported that DR risk, shown to be most influenced by DM duration and glycemia, was further increased by uncontrolled hypertension and male sex [8]. Similarly, another Taiwanese study that noted an increasing trend in DR prevalence found that the prevalence rate was higher among males over the age of 40 y compared to females [6]. In contrast, another recent study conducted in Taiwan showed that higher SBP and female sex were significant independent risk factors associated with DR prevalence in patients with T2DM [11]. Although we observed that the proportion of male patients with DR was significantly reduced compared to those without DR, no associations between sex and risk of DR onset or progression were observed in the present study.

Sheu et al. [11] recently reported that the most important factor associated with DR prevalence among T2DM patients in Taiwan was high HbA1c levels observed over a 7-year period [11]. Diabetic patients may show a wide variation in their long-term glycemic profiles despite having similar baseline HbA1c values [2]. That study demonstrated that HbA1c variability in T1DM patients was associated with increased cumulative incidence of DR and increased risk, which required laser treatment. This variability in long-term glycemia, which is demonstrated through intrapersonal SDs of quarterly HbA1c values, was shown to be a risk factor for DR progression in the 12-step severity scale of the Early Treatment of Diabetic Retinopathy Study [17]. Gerstein et al. [18] showed that more severe retinopathy at baseline was associated with higher baseline HbA1c and SBP, and myocardial infarction or stroke were also more likely in these patients. In fact, as retinopathy worsened over a 4-year period, the HbA1c and SBP also became progressively worse. Similarly, risk of DR progression increased with duration of diabetes and the extent of change in HbA1c [9].

In this study, we observed that updated mean HbA1c is associated with new-onset DR. Compared to baseline HbA1c which only one value measured, and may underestimate the importance of HbA1c as a risk factor [19], and that we did not detect any association with new-onset DR and DR progression, updated mean of HbA1c which using several values has been found to be a better tool [19, 20]. Since diabetes complications were continuous changes progress with time, updated mean of HbA1c may be a better risk factor to predict complications.

Early intensive control of glucose and blood pressure has been shown to prevent the onset of diabetic nephropathy [21]. A study that investigated the effects of changes in glycemic control and arterial blood pressure on the incidence of clinically significant macular edema in 1878 diabetic patients found that changes in metabolic control and systolic blood pressure *in any direction* were risk factors for progression to diabetic macular edema [9]. The noted study of participants followed for more than 30 years, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Control of Complications Study at 30 Years (DCCT/EDIC) [22], has set standards for the clinical management of T1DM and has looked at the relative time course of DR onset, established evidence-based frequency of DR screening. However, fairly recent data from a long-term study of kidney, eye and foot disease in diabetic patients revealed that current diabetes treatments are not adequate to prevent microvascular complications and the potential severe morbidity that may result [6].

One of the main strengths of the present study is the real-time follow-up of a large number of patients through the nationally sponsored Diabetes Shared-Care Program, adding to the credibility of our data and results. Nevertheless, the present study also has certain limitations, including that it was conducted in a single regional institution. In addition, the follow-up time varied depending upon when the patients first joined the Diabetes Shared-Care Program, which meant that numbers of visits and related data were greater in patients who enrolled earlier. Future prospective research is needed to corroborate the results of the present study in a larger cohort from multiple centers, and to

clearly differentiate metabolic and microvascular risk factors associated with new-onset DR and DR progression.

Conclusions

The risk factors associated with DR onset and progression are different. Whereas the presence of neuropathy and blood pressure were associated with both DR onset and progression, the risk of new-onset DR was also associated with updated mean of HbA1c and cholesterol.

Disclosure of conflict of interest

None.

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