

Discordance in risk factors for the progression of diabetic retinopathy and diabetic nephropathy in patients with type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: We aimed to investigate whether there are differences in the risk factors or markers for the progression of diabetic retinopathy (DR) and diabetic nephropathy (DN) in type 2 diabetes mellitus.

Materials and Methods: We carried out a 3-year retrospective cohort study of 604 patients with type 2 diabetes mellitus. The outcomes were the progression of DR (worsening of the DR stage) and DN (an estimated glomerular filtration rate decline >12%) at the 3-year follow up. The mean hemoglobin A1c (HbA1c) level and HbA1c variability (HbA1c-*VAR*) were calculated.

Results: The mean HbA1c and HbA1c-*VAR* levels were higher in the DR progressors ($n = 67$) than in the DR non-progressors ($n = 537$). The mean HbA1c was a significant predictor for DR progression independent of the duration of diabetes and HbA1c-*VAR* levels. The urine albumin-to-creatinine ratio at baseline and HbA1c-*VAR* levels were higher in the DN progressors ($n = 34$) than in the DN non-progressors ($n = 570$). The triglyceride to high-density lipoprotein cholesterol ratio at baseline tended to be higher in the DN progressors than in the DN non-progressors. HbA1c-*VAR* levels and the triglyceride-to-high-density lipoprotein cholesterol ratio were significant predictors for DN progression independent of estimated glomerular filtration rate and the urine albumin-to-creatinine ratio.

Conclusions: Average glycemia was significantly associated with progression of DR, whereas glycemic variability and dyslipidemia were significantly associated with progression of DN in type 2 diabetes mellitus.

INTRODUCTION

Diabetic retinopathy (DR) is a microvascular complication of diabetes and is the most frequent cause of blindness. Diabetic nephropathy (DN), or chronic kidney disease associated with diabetes, is characterized by albuminuria and progressive loss of renal function¹. It is well established that long-term exposure to hyperglycemia is the major risk factor for both DR and DN^{2,3}. Each complication has a strong impact on the initiation or progression of the other⁴.

However, the progression of DR and DN can be discordant in diabetes patients. During the Diabetes Control and

Complications Trial in type 1 diabetes mellitus patients, 12.9% of patients did not have DR progression, but had DN development; 10.7% had DR progression, but not DN development, and 7.3% had both DR progression and DN development⁴. In the Renal Insufficiency and Cardiovascular Events (RIACE) study, 41.4% of patients with type 2 diabetes mellitus and advanced DR showed no evidence of DN⁵. That cross-sectional study also showed that different risk factors or markers were associated with DN or DR. Subsequently, the RIACE study showed that glycemic variability over a long-term period could predict the presence of DN, but not of DR⁶. Recently, we reported that DN was present in ~60% of patients with type 2 diabetes mellitus who had advanced DR, and that glycemic

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variability and dyslipidemia were associated with the initiation and progression of DN in these patients⁷. Another study reported that systolic blood pressure (BP) variability predicted the initiation and progression of DN, but not DR, in patients with type 2 diabetes mellitus⁸.

All of these studies suggest that different risk factors might be involved in the pathogenesis of DR and DN. However, few longitudinal studies have addressed this issue. Therefore, we carried out the present study to investigate whether there are differences in the risk factors or markers for the progression of DR and DN in patients with type 2 diabetes mellitus.

METHODS

Study Design

Patients with type 2 diabetes mellitus who visited Yeouido St. Mary's Hospital, Seoul, Korea, from July 2013 to December 2013 were enrolled in the present retrospective, observational cohort study. Patients who had been diagnosed with type 2 diabetes mellitus for at least 1 year and were being followed up regularly at both the Department of Internal Medicine and Department of Ophthalmology were included. Patients with primary renal disease, advanced liver disease, cancer not in remission, secondary diabetes, an estimated glomerular filtration rate (eGFR; mL/min/1.73 m²) <30 or proliferative DR were excluded. The outcome was the progression of DR or DN after 3 years. This study was approved by the institutional review board of Yeouido St. Mary's Hospital.

Data Collection

The clinical and laboratory data of the study participants were collected from electronic medical records. Hypertension was defined as a systolic BP \geq 140 mmHg or diastolic BP \geq 90 mmHg or any use of BP-lowering medications. Cardiovascular disease included coronary artery disease or cerebrovascular disease. Dyslipidemia was defined as the use of a statin or fibrate. During follow up, glycated hemoglobin (HbA1c) and serum creatinine levels were measured every 3–6 months in each individual.

After an overnight fast, blood samples were obtained for analysis of serum concentrations of creatinine and lipid profiles. The HbA1c level was determined by high-performance liquid chromatography. Albuminuria was quantified by calculating the urine albumin-to-creatinine ratio (ACR; mg/g) in the urine, and eGFR was calculated using the Modification of Diet in Renal Disease study equation⁹.

The presence of DR was examined by two DR specialists at the Department of Ophthalmology. The stage of DR was graded as reported¹⁰: absent DR; mild, moderate or severe non-proliferative DR; and proliferative DR. The progression of DR was defined as worsening of the stage of DR.

The progression of DN was defined as an eGFR decline $>$ 12% at the 3-year follow up (4% per year)^{11–13}. The eGFR decline was calculated as follows: eGFR decline (%/year) = (eGFR at 3 year – eGFR at baseline) / 3 \times 100 (%).

An eGFR slope per year was also calculated after creating a linear regression model for time versus eGFR using the least-squares method.

Glycemic variability during follow up was measured. HbA1c variability (HbA1c-VAR) was calculated as the standard deviation (SD) of multiple HbA1c levels during follow up. To correct for differences in the number of HbA1c measurements, an "adjusted HbA1c-VAR" was calculated as HbA1c-VAR divided by square root of $[n/(n - 1)]$, where n was the number of HbA1c measurements¹⁴. To correct for large SDs due to high levels of mean HbA1c, the coefficient of variation of HbA1c (HbA1c-CV) was also calculated as the HbA1c-VAR divided by mean HbA1c level¹⁵.

Statistical Analysis

All statistical analyses were carried out with the use of SAS software (SAS Institute Inc., Cary, NC, USA). Data are expressed as mean \pm SD or medians (interquartile range [IQR]) for continuous variables, and as numbers (percentage) for categorical variables. Because triglyceride and urine ACR values are not normally distributed, these were analyzed after logarithmic transformation. The t -test was used to compare continuous variables. The numbers of categorical variables were compared with the use of the χ^2 -test or Fisher's exact test. Multivariate logistic regression analysis was carried out to assess the independent predictive effects of the variables on the risk for progression of DR or DN. P -values of $<$ 0.05 were considered to show statistical significance.

RESULTS

A total of 895 patients met the inclusion criteria. From these patients, we selected and analyzed the data for 604 patients who were followed up for 3 years. There was no difference in baseline clinical characteristics between 604 patients with follow up and 895 patients enrolled initially (Table S1).

A total of 68 patients (11%) showed progression of DR, including proliferative DR in six patients. Progressors of DR had a longer duration of diabetes, higher body mass index, more frequent history of hypertension and more frequent use of insulin compared with DR non-progressors (Table 1). The HbA1c level at baseline and the mean HbA1c level were higher in the DR progressors than in the DR non-progressors (7.70 ± 1.10 vs $7.27 \pm 1.03\%$, $P = 0.001$, and 7.72 ± 1.05 vs $7.27 \pm 0.96\%$, $P = 0.001$, respectively). Among three indices of HbA1c variability, HbA1c-VAR and adjusted HbA1c-VAR were higher in the progressors than in the non-progressors (0.63 ± 0.41 vs $0.52 \pm 0.33\%$, $P = 0.036$ for HbA1c-VAR; 0.59 ± 0.39 vs $0.49 \pm 0.31\%$, $P = 0.033$ for adjusted HbA1c-VAR). However, another index of HbA1c variability, HbA1c-CV, was not different between the progressors and non-progressors. Multiple logistic regression analysis that included the mean HbA1c level, HbA1c-VAR and duration of diabetes as independent variables showed that mean HbA1c level was a significant and independent predictor of the progression of DR

Table 1 | Clinical characteristics of study participants according to the progression of diabetic retinopathy

	Non-progressors (n = 536)	Progressors (n = 68)	P-value
Baseline			
Age (years)	60.7 ± 10.7	60.8 ± 11.4	0.967
Sex (female)	249 (46.5)	26 (38.2)	0.2
Duration of diabetes (years)	13.7 ± 8.4	16.3 ± 7.7	0.019
BMI (kg/m ²)	25.0 ± 3.5	26.1 ± 3.3	0.017
Smoking	83 (17.4)	17 (27.4)	0.055
Hypertension	333 (62.5)	52 (76.5)	0.024
ACEi or ARB use	281 (85.9)	46 (88.5)	0.623
Dyslipidemia	421 (78.5)	53 (77.9)	0.909
Insulin use	120 (22.4)	24 (35.3)	0.019
CVD	154 (28.7)	18 (26.5)	0.697
Hemoglobin (g/dL)	13.7 ± 1.6	13.8 ± 1.6	0.592
Systolic BP (mmHg)	126.4 ± 11.7	128.2 ± 10.0	0.229
Diastolic BP (mmHg)	73.8 ± 8.1	75.2 ± 7.5	0.189
HbA1c (%)	7.27 ± 1.03	7.70 ± 1.10	0.001
Triglyceride (mmol/L)	1.51 (1.11, 2.08)	1.31 (0.90, 1.91)	0.02
HDL cholesterol (mmol/L)	1.19 ± 0.27	1.23 ± 0.33	0.427
LDL cholesterol (mmol/L)	2.17 ± 0.57	2.04 ± 0.49	0.077
Triglyceride-to-HDL cholesterol ratio	3.5 ± 2.3	3.1 ± 1.9	0.153
eGFR (mL/min/1.73 m ²)	77.4 ± 16.0	78.8 ± 19.1	0.555
Urine ACR (mg/g)	12.9 (7.1, 32.4)	15.8 (8.1, 38.9)	0.639
Follow up			
Mean HbA1c (%)	7.27 ± 0.96	7.72 ± 1.05	0.001
HbA1c-VAR (%)	0.52 ± 0.33	0.63 ± 0.41	0.036
Adjusted HbA1c-VAR (%)	0.49 ± 0.31	0.59 ± 0.39	0.033
HbA1c-CV (%)	0.07 ± 0.04	0.08 ± 0.05	0.104
eGFR slope (mL/min/1.73 m ² per year)	5.17 ± 6.50	5.12 ± 4.04	0.923
eGFR decline (% per year)	5.17 ± 6.50	5.32 ± 5.84	0.853

Data are mean ± standard deviation, n (%) or median (interquartile range). ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin-converting enzyme receptor blocker; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HbA1c-CV, coefficient of variation of glycated hemoglobin; HbA1c-VAR, glycated hemoglobin variability; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2 | Multiple logistic regression analysis of risk factors influencing progression of diabetic retinopathy

Predictors	Odds ratio	95% CI	P-value
Mean HbA1c	1.35	1.02–1.78	0.033
HbA1c-VAR	1.57	0.71–3.45	0.264
Duration of diabetes	1.03	1.00–1.06	0.08

CI, confidence interval; HbA1c-VAR, glycated hemoglobin variability.

(Table 2). This result was similar after adjusting for eGFR, triglyceride-to-high-density lipoprotein (HDL) cholesterol ratio, the presence of DR, hypertension and use of an angiotensin-converting enzyme inhibitor or angiotensin-converting enzyme receptor blocker (Table S2).

A total of 34 patients (6%) showed the progression of DN, five of whom received hemodialysis. Progressors of DN were older, used insulin more frequently and smoked more

frequently than DN non-progressors (Table 3). The eGFR at the baseline was lower, and urine ACR at the baseline and HbA1c-VAR level were higher in the DN progressors than in the DN non-progressors (66.8 ± 22.7 vs 78.1 ± 15.7 mL/min/1.73 m², *P* = 0.007; 50.1 [IQR 8.9–676.1] vs 12.9 [IQR 7.1–30.9] mg/g, *P* < 0.001, and 0.73 ± 0.42 vs 0.52 ± 0.33%, *P* = 0.006, respectively). The other indices of HbA1c variability, adjusted HbA1c-VAR and HbA1c-CV, were also higher in the DN non-progressors. The triglyceride-to-HDL cholesterol ratio tended to be higher in the DN progressors than in the DN non-progressors (4.9 ± 4.2 vs 3.4 ± 2.1, *P* = 0.051). Multiple logistic regression analysis including HbA1c-VAR, triglyceride-to-HDL cholesterol ratio and eGFR or urine ACR at baseline as independent variables showed that HbA1c-VAR and the triglyceride-to-HDL cholesterol ratio were significant and independent predictors of the progression of DN (Table 4). This result was similar after adjusting for the duration of diabetes, mean HbA1c, presence of DR, hypertension and use of an

Table 3 | Clinical characteristics of study participants according to the progression of diabetic nephropathy

	Non-progressors (<i>n</i> = 570)	Progressors (<i>n</i> = 34)	<i>P</i> -value
Baseline			
Age (years)	60.5 ± 10.9	64.7 ± 8.1	0.006
Sex (female)	263 (46.1)	12 (35.3)	0.217
Duration of diabetes (years)	14.0 ± 8.3	14.6 ± 8.9	0.665
BMI (kg/m ²)	25.1 ± 3.5	25.2 ± 3.9	0.831
Smoking	88 (17.3)	12 (37.5)	0.004
Hypertension	360 (63.5)	25 (73.5)	0.236
ACEi or ARB use	305 (86.2)	22 (88.0)	0.796
Dyslipidemia	445 (78.1)	29 (85.3)	0.319
Insulin use	125 (21.9)	19 (55.9)	<0.0001
CVD	158 (27.7)	14 (41.2)	0.091
Hemoglobin (g/dL)	13.7 ± 1.6	13.2 ± 1.6	0.095
Systolic BP (mmHg)	126.5 ± 11.5	128.2 ± 11.8	0.403
Diastolic BP (mmHg)	74.0 ± 8.0	73.5 ± 7.4	0.731
HbA1c (%)	7.30 ± 1.05	7.52 ± 1.03	0.24
Triglyceride (mmol/L)	1.49 (1.08, 2.04)	1.61 (1.11, 3.09)	0.071
HDL cholesterol (mmol/L)	1.20 ± 0.23	1.10 ± 0.24	0.045
LDL cholesterol (mmol/L)	2.16 ± 0.54	2.24 ± 0.85	0.564
Triglyceride to HDL cholesterol ratio	3.4 ± 2.1	4.9 ± 4.2	0.051
eGFR (mL/min/1.73 m ²)	78.1 ± 15.7	66.8 ± 22.7	0.007
Urine ACR (mg/g)	12.9 (7.1, 30.9)	50.1 (8.9, 676.1)	0.0003
Follow up			
Mean HbA1c (%)	7.33 ± 0.98	7.25 ± 0.92	0.671
HbA1c-VAR (%)	0.52 ± 0.33	0.73 ± 0.42	0.006
Adjusted HbA1c-VAR (%)	0.49 ± 0.31	0.69 ± 0.39	0.006
HbA1c-CV (%)	0.07 ± 0.04	0.10 ± 0.06	0.004
eGFR slope (mL/min/1.73 m ² per year)	5.71 ± 4.21	-5.64 ± 4.50	<0.0001
eGFR decline (% per year)	6.08 ± 5.16	-9.88 ± 6.85	<0.0001

Data are mean ± standard deviation, *n* (%) or median (interquartile range). BMI, body mass index; ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin-converting enzyme receptor blocker; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HbA1c-CV, coefficient of variation of glycated hemoglobin; HbA1c-VAR, glycated hemoglobin variability; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

angiotensin-converting enzyme inhibitor or angiotensin-converting enzyme receptor blocker (Table S3).

There were 31 progressors of DN alone, 65 progressors of DR alone, and three progressors of both DN and DR. DN-alone progressors were older and used insulin more frequently than DR-alone progressors (Table 5). The urine ACR at baseline was higher, and eGFR at baseline was lower in the DN-alone progressors than in the DR-alone progressors: 53.7 (IQR 16.6–776.2) versus 15.8 (IQR 8.3–37.1) mg/g, *P* = 0.001, for urine ACR level, and 67.6 ± 21.9 versus 79.7 ± 18.1 mL/min/1.73 m², *P* = 0.005, for eGFR. The triglyceride-to-HDL cholesterol ratio at baseline was higher in the DN-alone progressors than in the DR-alone progressors: 5.1 ± 4.3 versus 3.1 ± 1.9, *P* = 0.023. The mean HbA1c level during the follow-up period was lower in the DN-alone progressors than in the DR-alone progressors: 7.23 ± 0.85 versus 7.73 ± 1.03%, *P* = 0.021. However, indices of HbA1c variability during the follow-up period did not differ significantly between the two groups. Multiple logistic regression analysis that included the duration of

Table 4 | Multiple logistic regression analysis of risk factors influencing the progression of diabetic nephropathy

Predictors	Odds ratio	95% CI	<i>P</i> -value
Model 1			
HbA1c-VAR	3.02	1.28–7.10	0.012
Triglyceride-to-HDL cholesterol ratio	1.15	1.02–1.29	0.026
eGFR	0.96	0.94–0.98	0.0003
Model 2			
HbA1c-VAR	2.59	1.01–6.64	0.048
Triglyceride-to-HDL cholesterol ratio	1.12	0.97–1.28	0.112
Urine ACR	3.82	2.30–6.34	<0.0001

ACR, albumin-to-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c-VAR, glycated hemoglobin variability; HDL, high-density lipoprotein.

diabetes, presence of DR, hypertension and use of an angiotensin-converting enzyme inhibitor or angiotensin-converting enzyme receptor blocker as independent variables showed that

Table 5 | Clinical characteristics of study participants according to the progression of diabetic nephropathy alone and diabetic retinopathy alone

	DN alone (n = 31)	DR alone (n = 65)	P-value
Baseline			
Age (years)	64.7 ± 7.9	60.6 ± 11.4	0.043
Sex (female)	11 (35.5)	25 (38.4)	0.778
Duration of diabetes (years)	14.9 ± 9.3	16.5 ± 7.8	0.399
BMI (kg/m ²)	24.8 ± 3.9	25.9 ± 3.3	0.164
Smoking	11 (37.9)	16 (27.1)	0.301
Hypertension	22 (71.0)	49 (75.4)	0.645
ACEi or ARB use	20 (90.9)	44 (89.8)	1
Dyslipidemia	26 (83.9)	50 (76.9)	0.433
Insulin use	18 (58.1)	22 (35.4)	0.036
CVD	12 (38.7)	15 (24.6)	0.155
Hemoglobin (g/dL)	13.2 ± 1.6	13.8 ± 1.5	0.097
Systolic BP (mmHg)	128.4 ± 11.3	128.3 ± 9.6	0.948
Diastolic BP (mmHg)	73.4 ± 7.5	75.2 ± 7.5	0.275
HbA1c (%)	7.5 ± 1.0	7.7 ± 1.1	0.39
Triglyceride (mmol/L)	1.61 (1.20, 3.19)	1.32 (0.95, 1.91)	0.016
HDL cholesterol (mmol/L)	1.10 ± 0.22	1.23 ± 0.33	0.024
LDL cholesterol (mmol/L)	2.24 ± 0.88	2.03 ± 0.49	0.232
Triglyceride-to-HDL cholesterol ratio	5.1 ± 4.3	3.1 ± 1.9	0.023
eGFR (mL/min/1.73 m ²)	67.6 ± 21.9	79.7 ± 18.1	0.005
Urine ACR (mg/g)	53.7 (16.6, 776.2)	15.8 (8.3, 37.1)	0.001
Follow up			
Mean HbA1c (%)	7.23 ± 0.85	7.73 ± 1.03	0.021
HbA1c-VAR (%)	0.71 ± 0.41	0.61 ± 0.40	0.271
Adjusted HbA1c-VAR (%)	0.67 ± 0.39	0.58 ± 0.38	0.269
HbA1c-CV (%)	0.10 ± 0.06	0.08 ± 0.05	0.092
eGFR slope (mL/min/1.73 m ² per year)	-5.70 ± 4.7	5.60 ± 3.47	<0.0001
eGFR decline (% per year)	-9.87 ± 7.03	6.02 ± 4.83	<0.0001

Data are mean ± standard deviation, *n* (%) or median (interquartile range). ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin-converting enzyme receptor blocker; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DN, diabetic nephropathy; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HbA1c-CV, coefficient of variation of glycated hemoglobin; HbA1c-VAR, glycated hemoglobin variability; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

the mean HbA1c, triglyceride-to-HDL cholesterol ratio and urine ACR or eGFR at baseline were significant and independent predictors of the progression of DN alone (Table S4).

DISCUSSION

The present 3-year retrospective, observational cohort study provides evidence that different factors were associated with the progression of DR and DN in patients with type 2 diabetes mellitus. The mean HbA1c level was a risk factor for the progression of DR independent of the duration of diabetes and HbA1c variability, whereas HbA1c variability and the triglyceride-to-HDL cholesterol ratio were risk factors for the progression of DN independent of eGFR and urine ACR.

Long-term glycemic control, expressed as the HbA1c level, is crucial for preventing the initiation and progression of both DR and DN¹. HbA1c variability is another risk factor that is related to chronic hyperglycemia, and is expressed as the SD of serially measured HbA1c levels^{14,16}. In patients with type 1 diabetes

mellitus, HbA1c variability is an independent risk factor for DR and DN^{14,15,17}. In patients with type 2 diabetes mellitus, HbA1c variability is associated with the initiation of DN, such as microalbuminuria and decreased GFR^{5,18–21}. Although the reason for the harmful effects of HbA1c variability on the development of DR or DN are not clear, one possible mechanism involves “metabolic memory” from repeated exposure to glycaemic instability²², which can lead to increased oxidative stress²³.

Factors that increase the risk of or are associated with DR are the duration of diabetes, level of glycaemic control, DN, hypertension and dyslipidemia²⁴. In the present study, DR progressors had a higher HbA1c level at baseline, and a higher mean HbA1c level and longer duration of diabetes than DR non-progressors. Two of the three indices of HbA1c variability were higher in the DR progressors than in the DR non-progressors. However, the mean HbA1c level alone was a significant predictor of DR progression after adjusting for HbA1c-VAR and duration of diabetes. Most studies have reported that

HbA1c variability is an independent risk factor for DR in type 1 diabetes mellitus, but not type 2 diabetes mellitus^{14,15,17,25}.

DN is the leading cause of end-stage renal disease. It is often accompanied by DR, as the pathogenesis of both complications is related to chronic hyperglycemia. However, some patients do not show any phenotype of DN, even in the presence of proliferative DR. Phenotypes of DN are renal dysfunction (eGFR <60 mL/min/1.73 m²), albuminuria (urine ACR >30 mg/g creatinine) or both²⁶. In the present study, we defined the progression of DN as an eGFR decline >4% per year, in accordance with previous studies^{11–13}, because there is no definite criterion for the progression of DN. At baseline, as expected, eGFR was lower and urine ACR was higher in the DN progressors than in the DN non-progressors. All three indices of HbA1c variability were also higher in the DN progressors. HbA1c-VAR was a significant predictor of DN progression, even after adjusting for eGFR, urine ACR and the triglyceride-to-HDL cholesterol ratio. These findings are consistent with those of previous studies^{5,18–21}. Recently, we also reported that HbA1c variability was significantly associated with urine ACR and eGFR, and was an independent predictor of the presence of DN (urine ACR >30 mg/g and eGFR <60 mL/min/1.73 m²) in patients with advanced DR⁷. These results are consistent with those of the RIACE study, showing that HbA1c variability affected albuminuric DN more than average HbA1c level did⁶. Of note, HbA1c variability was not an independent predictor of DR in the RIACE study, as in the present study.

Dyslipidemia exists frequently in patients with type 2 diabetes mellitus, and plays a critical role in the pathogenesis of atherosclerotic cardiovascular disease. High triglyceride and low HDL cholesterol levels are hallmarks of diabetic dyslipidemia²⁷. Studies have reported that a lower HDL cholesterol level is associated with DN in type 2 diabetes patients^{28–30}. In particular, the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation study³¹ showed that a lower HDL cholesterol level was a risk factor predicting the initiation and progression of DN, whereas it was not a risk factor for DR. The deleterious effect of low HDL cholesterol level on the progression of DN could be explained by the fact that HDL plays a protective role in renal damage by reducing oxidative stress and inflammation^{32,33}. High triglyceride level might influence the progression of DR and DN. The Fenofibrate Intervention and Event Lowering In Diabetes study³⁴ and Action to Control Cardiovascular Risk in Diabetes trial³⁵ showed that a fenofibrate-induced decrease in triglyceride level has favorable effects on the progression of DR. In addition, the Fenofibrate Intervention and Event Lowering In Diabetes study and the Diabetes Atherosclerosis Intervention Study showed that fenofibrate reduces albuminuria and slows the decline in eGFR^{36,37}. Therefore, it is not unpredictable that low HDL cholesterol and high triglyceride levels are independent risk factors for the development of albuminuria and DN in patients with type 2 diabetes mellitus^{29,38}. Consistent with the preceding

studies, in the present study, the triglyceride-to-HDL cholesterol ratio tended to be higher in the DN progressors than in the DN non-progressors, and was a significant predictor of DN progression even after adjusting for eGFR and HbA1c-VAR.

Finally, comparison of clinical characteristics between DN-alone progressors and DR-alone progressors confirmed that mean HbA1c level was more strongly associated with DR progression, whereas the triglyceride-to-HDL cholesterol ratio and urine ACR or eGFR levels were more strongly associated with DN progression.

The current study had a few limitations. First, it had a retrospective design and no causality could be ascertained. Second, outcomes were infrequent, as the follow-up duration was relatively short and duration of diabetes was heterogeneous. Third, DN progression was defined as the eGFR decline only. The initiation and progression of albuminuria were not included in the definition of DN progression, because urine ACR was not measured in every patient during the follow-up period.

In conclusion, the present study showed that average HbA1c level was a risk factor for the progression of DR independent of the duration of diabetes and HbA1c variability, whereas HbA1c variability and dyslipidemia were risk factors for the progression of DN independent of eGFR and urine ACR. However, long-term prospective studies are required to confirm the discordance in risk factors for the progression of DR and DN in patients with type 2 diabetes mellitus in the future.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Baseline clinical characteristics of study participants.

Table S2 | Multiple logistic regression analysis of risk factors influencing the progression of diabetic retinopathy.

Table S3 | Multiple logistic regression analysis of risk factors influencing the progression of diabetic nephropathy.

Table S4 | Multiple logistic regression analysis of risk factors influencing the progression of diabetic nephropathy alone.