Development and Progression of Diabetic Retinopathy and Associated Risk Factors in Korean Patients with Type 2 Diabetes: The Experience of a Tertiary Center

Yoon Jeon Kim, June-Gone Kim, Joo Yong Lee, Kyoong Sub Lee, Soo Geun Joe, Joong-Yeol Park, Min-Seon Kim, and Young Hee Yoon

INTRODUCTION

Diabetes mellitus (DM) is a major health problem worldwide, and is one of the most common and rapidly increasing chronic diseases. The prevalence of diabetes for all age groups worldwide was estimated to be 2.8% in 2000 and is predicted to reach 4.4% in 2030, meaning that the total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 (1). This increasing prevalence is due to an aging population, changes in lifestyle with economic development, and increasing rates of obesity associated with decreased physical activity (2). The prevalence of diabetes has also increased rapidly in Korea. Estimated to be 7.6% in 2001, the prevalence of diabetes rose to 9.1% of the adult population according to an analysis of the 2005 Korea National Health and Nutrition Examination Survey (KNHANES), with a prevalence of impaired fasting glucose of 17.4% (3). The economic burden continues to rise and, according to the KNHANES, the aggregate annual direct cost of diabetes in Korea was 260 million USD in 2009 (4, 5).

Diabetes is always associated with long-term complications. Diabetic retinopathy (DR) is the leading cause of blindness among working-aged adults worldwide. The prevalence of any DR and vision-threatening DR were variably reported as 15.8%–46.9% and 4.6%–10%, respectively, showing that considerable numbers of patients are at risk of DR (6). Although early retinopathy does not have a significant effect on vision, it can progress to a more advanced stage, termed proliferative DR (PDR), putting patients at a substantially increased risk of serious complications that can result in permanent vision loss. Therefore, prevention, early detection, and effective management of DR and the identification of associated risk factors are very important for diabetes care to improve public health and ease the financial burden (5).

Several large population-based studies, including the Diabetes Control and Complications Trial (DCCT), the UK Prospective Diabetes Study (UKPDS), the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, have identified other risk factors associated with the development or progression of DR (7-11). From the results of these studies, age, sex, socioeconomic status, and comorbid systemic arterial hypertension are considered important determinants of retinopathy risk. On the other hand, one study showed that metabolic control as measured by HbA1c and disease duration accounts for only 11% of the risk of DR, leaving 89% of the risk of the development of DR to other factors (12). As these variables are time and ethnici-
ty dependent (13), an analysis based on recent data in Koreans is required. Although there have been several cross-sectional studies regarding the prevalence and associated risk factors in Korea (6, 14, 15), cohort studies on the development and progression of DR in recent decades are not available, to our knowledge. The purpose of this study was to explore the incidence of and risk factors for the development of DR and progression to PDR in Korean patients with type 2 DM since 2000.

**MATERIALS AND METHODS**

Patients who were diagnosed with type 2 DM and followed for more than 5 yr annually or more often at a hospital-based diabetic clinic (Asan Medical Center, Seoul, Korea) were selected by medical record review in a consecutive manner. In this retrospective cohort study, patients with PDR at the initial examination, with concomitant ocular disease other than DR, or history of ocular trauma or intraocular surgery were excluded. If the patient became pregnant or underwent intravitreal anti-vascular endothelial growth factor (VEGF) or steroid injections, only data obtained during the period before the event were analyzed. At baseline, a detailed medical history, including previous treatment for diabetes, hypertension, smoking habits, and alcoholic intake, was taken. At baseline and every visit, arterial blood pressure (BP), body weight, and height were measured, and blood tests, including plasma glucose, HbA1c, and lipid profiles, were performed. Urine tests were also performed and urine albumin-to-creatinine ratios (UACR) were used in the analysis. Body weight and height were used to calculate the body mass index (BMI), which was used for analysis; diabetes medication information was described. Patients were followed every 3 or 6 months depending on their glucose control.

At their initial visit and at each visit to a retina clinic, all patients underwent a comprehensive ophthalmologic examination that included a review of their ophthalmologic history, measurement of visual acuity and intraocular pressure (IOP), slit lamp biomicroscopy, and funduscopic examinations through dilated pupils by retinal specialists. DR was evaluated on the basis of fundus photography taken on every patient at every visit. When necessary, fluorescein angiography was performed to assess vascular abnormalities and the extent of the capillary nonperfusion area. The frequency of the eye examination was at least once a year or more, determined by the ophthalmologist depending on the degree of DR. The degree of DR was classified into 5 stages by the following criteria of the Early Treatment Diabetic Retinopathy Study (ETDRS): 1) no diabetic retinopathy—“no DR”; 2) mild nonproliferative diabetic retinopathy—“mild NPDR”; 3) moderate nonproliferative diabetic retinopathy—“moderate NPDR”; 4) severe nonproliferative diabetic retinopathy—“severe NPDR”; and 5) proliferative diabetic retinopathy—“PDR”. If both eyes were rated at different stages, the grade of the worse eye was used.

Based on the DR classification at the initial and final visits, the development of DR and progression to PDR were defined as follows: 1) the development of any type of DR in the patients who were free of DR at baseline—“development of DR”; and 2) the progression to PDR in patients who had NPDR at baseline—“progression to PDR”. The incidences of the development of DR and progression to PDR were defined as the number of patients with those events divided by the total sum of person-years of the follow-up period.

**Statistical analysis**

Patients with no DR and NPDR at baseline were divided into 2 groups according to the development of DR and progression to PDR, respectively. Descriptive statistics (number and percentage of each categorical variable and the mean ± standard deviation [SD] of each continuous variable) were evaluated to determine the demographic and ocular baseline characteristics of each group. As for repeatedly measured medical values, both the baseline value and the mean during the follow-up period were used in the analysis. To analyze the long-term fluctuation of blood glucose, the SDs of all HbA1c measurements were calculated in each patient. Normally distributed data were compared between the 2 groups by using an unpaired t-test. Non-normally distributed data were compared using a Mann-Whitney U test. To compare categorical data, the chi-square test of the Fisher’s exact test was used as appropriate on the basis of the data distribution. Hazard ratios (HRs) for associations among potential risk factors for the development of DR and progression to PDR were obtained using a Cox’s proportional hazards model. Univariate analyses were performed separately for each variable. Variables with a probability value of 0.2 in univariate analysis were considered significant and were included in a multivariate Cox proportional hazards model. A backward elimination process was used to develop the final multivariate model, and adjusted HRs with 95% confidence intervals (CIs) were calculated. Schoenfeld residuals and the log (-log [survival rate]) test were used to verify that proportional hazards assumptions were not violated. Model fit was assessed using residual analyses. All statistical analyses were performed using SAS version 9.1 software (SAS Institute Inc., Cary, NC, USA) and SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA).

**Ethics statement**

This study was approved by the institutional review board of Asan Medical Center, University of Ulsan (IRB No. 2014-0124).

**RESULTS**

**Cohort characteristics**

A cohort consisting of 452 patients was developed which con-
secutively enrolled Korean patients diagnosed with type 2 DM and followed them for more than 5 yr. Among them, 371 patients were included in the final analysis, excluding 49 patients with PDR (10.8%) and 32 patients with history of intraocular surgery (7.1%). The mean patient age at baseline was 56.2 ± 12.2 yr (range, 34-75) and the mean follow-up period was 6.2 ± 1.9 yr (range, 5.0-13.0). At baseline, 140 patients showed no DR (37.7%), and 152 (41.0%), 40 (10.8%), and 39 (10.5%) patients showed mild NPDR, moderate NPDR, and severe NPDR, respectively. At the last follow-up, 110 patients remained in the no DR group (29.6%), and 104 (28.0%), 75 (20.2%), 45 (12.1%), and 37 (10.0%) patients showed mild NPDR, moderate NPDR, severe NPDR, and PDR, respectively (Fig. 1). Of 45 patients with severe NPDR at the last follow-up, 23 patients (51.1%) underwent panretinal photocoagulation during the follow-up period. During the cohort period, 1 patient became pregnant and 43 patients underwent intravitreal anti-VEGF or steroid injections. For these 44 patients, thus, only the data previous to the events were included in the analysis.

The rate of development of DR and associated risk factors

Of 140 patients who had no DR at baseline, 30 developed DR in 6.6 ± 1.6 yr of follow-up, resulting in a rate of development of DR of 32.1/1,000 person-years. Among 30 patients who developed DR, 16 (53.3%), 9 (30%), 3 (10%), and 2 (6.7%) patients progressed to mild NPDR, moderate NPDR, severe NPDR, and PDR, respectively. When the clinical characteristics were compared between the 2 groups in terms of the development of DR, the duration of diabetes at baseline was significantly longer in patients who developed DR (P < 0.001; Table 1). Regarding HbA1c, the baseline value (P = 0.155) and the SD of data obtained during the follow-up period (not shown in Table: 1.3 ± 0.9 vs. 1.1 ± 0.8 [developed DR vs. remained normal], P = 0.162) did not differ between the 2 groups. The mean during the follow-up period was higher in patients who developed DR (P = 0.045). In multivariate Cox proportional hazards analysis, a longer duration of diabetes at baseline (HR = 1.130, P = 0.010) and a higher mean HbA1c level (HR = 1.163, P = 0.006) were significant risk factors for the development of DR (Table 2). None of age, BP, cholesterol, triglycerides, HDL, and LDL cholesterol variables was a significant risk factor for development of DR.

The rate of progression to PDR and associated risk factors

Of 231 patients who had NPDR at baseline, 35 developed PDR in 5.6 ± 2.9 yr of follow-up, resulting in a rate of progression to PDR of 26.2/1,000 person-years. Besides, among 140 patients who were free of DR at baseline, 2 progressed to PDR in 8 and 9.5 yr of follow-up. In a comparison between nonprogressors and progressors, progressors had a higher UACR at baseline.

### Table 1. Comparison of clinical characteristics between the 2 groups in terms of the development of diabetic retinopathy (DR)

| Parameters                  | At baseline      | The mean value during follow-up |
|-----------------------------|------------------|---------------------------------|
|                            | Non-development of DR (n = 110) | Development of DR (n = 30) | P value | Non-development of DR (n = 110) | Development of DR (n = 30) | P value |
| Age (yr)                    | 53 ± 10          | 56 ± 8                          | 0.030    | 23.5 ± 3.3                       | 24.0 ± 2.7                  | 0.403   |
| Duration of DM (yr)         | 7 ± 5            | 13 ± 6                          | < 0.001  | 160.6 ± 50.4                     | 172.8 ± 54.0                | 0.135   |
| BMI (kg/m²)                 | 24.9 ± 3.4       | 25.2 ± 2.9                      | 0.625    | 7.5 ± 1.5                        | 8.3 ± 2.2                   | 0.045   |
| FBS (mg/dL)                 | 183.6 ± 52.2     | 180.0 ± 54.0                    | 0.505    | 138 ± 37                         | 134 ± 26                    | 0.355   |
| HbA1c (%)                   | 9.1 ± 2.0        | 9.3 ± 2.2                       | 0.155    | 82 ± 8                           | 83 ± 8                      | 0.651   |
| Systolic BP (mmHg)          | 140 ± 27         | 137 ± 22                        | 0.785    | 212.7 ± 38.7                     | 208.8 ± 69.6                | 0.326   |
| Diastolic BP (mmHg)         | 82 ± 8           | 85 ± 10                         | 0.851    | 194.9 ± 110.1                    | 201.7 ± 105.1               | 0.350   |
| Cholesterol (mg/dL)         | 216.5 ± 50.3     | 212.7 ± 73.5                    | 0.556    | 42.5 ± 15.5                      | 38.7 ± 11.6                 | 0.213   |
| Triglycerides (mg/dL)       | 196.0 ± 85.1     | 211.4 ± 100.6                   | 0.650    | 132.1 ± 95.5                     | 136.2 ± 109.9               | 0.325   |
| HDL cholesterol (mg/dL)     | 42.5 ± 7.7       | 42.5 ± 11.6                     | 0.450    | 20/75/10                         | 20/75/10                    | 0.250   |
| LDL cholesterol (mg/dL)     | 140.2 ± 88.2     | 149.5 ± 109.5                   | 0.226    | 12/26/62                        | 13/23/64                    | 0.957   |
| UACR (mg/g)                 | 28.9 ± 23.2      | 32.2 ± 24.6                     | 0.325    | 34 (31.0)                        | 12 (40)                     | 0.347   |
| Insulin/OHA/Diet only (%)   | 15/70/15         | 20/75/10                        | 0.250    | 34 (31.0)                        | 12 (40)                     | 0.347   |
| Current/Former/Never smoker (%) | 12/26/62       | 13/23/64                        | 0.957    |
| HTN medication (No. [%])    | 32 (31.0)        | 12 (40)                         | 0.347    |

DM, diabetes mellitus; BMI, body mass index; FBS, fasting blood sugar; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; UACR, urine albumin-to-creatinine ratio; OHA, oral hypoglycemic agent; HTN, hypertension.
than nonprogressors ($P < 0.001$) (Table 3). Regarding HbA1c, the baseline value did not differ between the 2 groups, such as in terms of the progression to PDR ($P = 0.195$). However, the mean ($P = 0.015$) and the SD (not shown in Table: $1.6 \pm 1.0$ vs. $1.2 \pm 0.7$ [progressors vs. non-progressors]) of the HbA1c data obtained during the follow-up period were higher in patients who progressed to PDR. In multivariate Cox proportional hazards analysis, a higher mean HbA1c level ($HR = 1.190, P = 0.005$), a higher SD of HbA1c ($HR = 1.160, P = 0.005$), and a higher UACR ($HR = 1.160, P = 0.005$) were significant risk factors for progression to PDR (Table 2). None of age, BP, cholesterol, triglycerides, HDL, and LDL cholesterol variables was a significant risk factor for progression to PDR.

**DISCUSSION**

In our current study, the development of DR and progression to PDR and associated risk factors in Koreans were examined...
based on the experiences at our tertiary institution. In patients receiving regular care and management of diabetes, the rate of development to DR from no DR was 32.1/1,000 person-years, and the rate of progression from NPDR to PDR was 26.2/1,000 person-years. These incidence rates were slightly lower than the 44.4/1,000 person-years rate of development of DR and the 37.5/1,000 person-years rate of progression to PDR reported by Kim et al. (16), who studied the rates of progression of DR in Koreans with type 2 diabetes in a similar manner in our center from 1990 to 1996. Baseline HbA1C level was 11.2-11.5%, which was also higher than our current study. It is not accurate, of course, to simply compare the results of different studies based on participants with unequal baseline DRs and socioeconomic backgrounds with different follow-up frequencies. However, the recent decreasing trend in diabetic micro-vascularopathy can be seen in other previous reports (17). In a previously published meta-analysis that reviewed the rates of progression of DR, rates of progression to PDR and severe visual loss were lower among participants in 1986-2008 than in 1975-1985, showing that diabetic patients have lower rates of progression since 1985 (18). By generating a more precise estimate of the prevalence of DR and its relationship with major modifiable risk factors based on many previous large-scale studies, public health education and awareness have improved and the optimal clinical prevention and management of DR could be possible, ultimately lowering the incidence rate of DR and related complications (8, 10, 11).

It is well known that inadequate glycemic control highly correlates with both the development and progression of DR in previous studies (7-11, 16). Our current findings confirmed these observations and showed that a higher HbA1c is independently associated with an increased risk of DR, i.e. for every 1% increase in HbA1c, the risk of DR development increased 1.16-fold (16%) and the risk of progression to PDR increased 1.19-fold (19%). Whereas the fasting blood sugar and HbA1c values at baseline did not differ in terms of the development of DR or progression to PDR, the mean HbA1c concentration was higher in patients who developed DR and progressed to PDR. This result is in line with many earlier reports that demonstrated that a long-lasting high blood glucose level could aggravate DR and, meanwhile, that strict glucose control could slow the rates of DR development and progression in patients with previously poor glycemic control (16, 19). Of note, the SD of HbA1c, which is considered to show the long-term fluctuation in glycemic control, was significantly higher in the progressor group. Although some previous studies demonstrated that variability in the HbA1c was a risk factor for diabetes-related microvascular diseases, there are still inconsistent results for its correlation with DR in type 2 DM (20). The duration of diabetes, which is related to the duration of high glucose levels, is an important risk factor for DR (21). Rema et al. (22) reported that for every 5-yr increase in the duration of diabetes, the risk of DR increased 1.89-fold. In our present study, for every 1 yr increase, the risk of DR increased by 1.13-fold (13%). Therefore, emphasizing continuous follow-up for DR assessment is important for diabetic patients.

DR and diabetic nephropathy are the 2 major diabetic microvascular complications and the most important causes of blindness and end-stage renal disease in Korea (3). Our findings suggest that patients with diabetic nephropathy show a more rapid progression to PDR, which is in line with the results of most previous studies (23). Albuminuria is one of the indicators of generalized microvascular disease in diabetic patients and is therefore a risk factor for combination DR (24). Nonetheless, inconsistent data also have been reported. In patients with type 2 diabetes, the association between nephropathy and retinopathy is less predictable than that of type 1 diabetes (14). In our present study, after adjustment for other risk factors, patients with albuminuria showed an increased risk of progression to PDR. Thus, more careful ophthalmologic follow-up is recommended when albuminuria develops in patients with DR.

Other significant risk factors for the development of DR and progression to PDR in previous studies were a younger age at DM diagnosis (21), male sex (25), hypertension (19, 23), high systolic BP (26), low diastolic BP (21), hypercholesterolemia (27), anemia (27), elevated systemic neutrophil count (28), use of insulin (29), high waist-to-hip ratio (21), smoking status, and diabetic foot disease (30). In our current study of Korean patients, age, sex, BP, hyperlipidemia, and smoking status did not correlate with DR progression (P > 0.05); caloric intake, blood cell count, and diabetic foot disease were not included in our analyses. Some of these differences might be explained that most of our study cohort was in good control of BP and hyperlipidemia. And some might be due to unique characteristics of Korean patients in that a significant portion of Korean diabetic patients are nonobese with type 2 DM, and their body weights often decrease during the disease course (6).

This study has several limitations in terms of generalizing the natural course of DR because it was a tertiary clinic-based study. It is quite possible that only patients with poorly controlled diabetes or a more severe form of diabetes with complications attend our hospital-based tertiary medical center. The mean baseline HbA1c level of study participants was relatively high, indicating this cohort consisted of poorly controlled diabetic patients. In addition, patients with severe forms of diseases generally tend to follow for a longer period. Taken together, the inclusion of patients with poor glycemic control may have overestimated the incidence of DR and PDR. On the other hand, this setting makes it possible to maintain a greater portion of patients who are more concerned about their health and adopt a more active attitude to the control of chronic diseases, such as diabetes. Byun et al. (5) recently reported that socioeconomic factors, including occupation, family income, and education, were associated with the frequency of screening for diabetic complica-
tions. In other words, patients with less education or low family income underwent less frequent screening for retinopathy or nephropathy. Thus, the participants of this study who had regular check-ups in the tertiary clinic are considered to have better compliance for screening and management of DR and show lower rates of diabetic complications than the general population. Moreover, patients with high-risk severe NPDR undergo panretinal photocoagulation treatment in most cases, affecting the natural history of DR progression. Therefore, when interpreting the results of our current study, these possible sources of bias should be considered. Large-scale population-based longitudinal studies are needed to examine the natural history of the development of DR and progression to PDR in Korean diabetic patients.

In conclusion, the rates of the development of DR and progression to PDR in Koreans with type 2 diabetes are lower than those reported over the last decade. And this study shows traditional, known risk-factors are still the most influential in the development and progression of DR in cohort of Korean patients with type 2 DM. Poor glycemic control is the common risk factor for the development of DR and progression to PDR. In addition, a longer duration of diabetes and a combination with diabetic nephropathy are significant risk factors for the development of DR and progression to PDR, respectively. Our findings may be used as a reference when planning screening tests and the subsequent follow-up of DR in Koreans with type 2 DM.
demographic Study of Diabetic Retinopathy. IX. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol 1989; 107: 237-43.

20. Kilpatrick ES, Rigby AS, Atkin SL. A1C variability and the risk of microvascular complications in type 1 diabetes: data from the Diabetes Control and Complications Trial. Diabetes Care 2008; 31: 2198-202.

21. Porta M, Sjoelie AK, Chaturvedi N, Stevens L, Rottiers R, Veglio M, Fuller JH; EURODIAB Prospective Complications Study Group. Risk factors for progression to proliferative diabetic retinopathy in the EURODIAB Prospective Complications Study. Diabetologia 2001; 44: 2203-9.

22. Rema M, Premkumar S, Anitha B, Deepa R, Pradeepa R, Mohan V. Prevalence of diabetic retinopathy in urban India: the Chennai Urban Rural Epidemiology Study (CURES) eye study, I. Invest Ophthalmol Vis Sci 2005; 46: 2328-33.

23. Roy MS, Affouf M. Six-year progression of retinopathy and associated risk factors in African American patients with type 1 diabetes mellitus: the New Jersey 725. Arch Ophthalmol 2006; 124: 1297-306.

24. Alzaid AA. Microalbuminuria in patients with NIDDM: an overview. Diabetes Care 1996; 19: 79-89.

25. Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, Ferris FL 3rd, Klein R; American Diabetes Association. Retinopathy in diabetes. Diabetes Care 2004; 27: S84-7.

26. Teuscher A, Schnell H, Wilson PW. Incidence of diabetic retinopathy and relationship to baseline plasma glucose and blood pressure. Diabetes Care 1988; 11: 246-51.

27. Aiello LP, Cahill MT, Wong JS. Systemic considerations in the management of diabetic retinopathy. Am J Ophthalmol 2001; 132: 760-76.

28. Woo SJ, Ahn SJ, Ahn J, Park KH, Lee K. Elevated systemic neutrophil count in diabetic retinopathy and diabetes: a hospital-based cross-sectional study of 30,793 Korean subjects. Invest Ophthalmol Vis Sci 2011; 52: 7697-703.

29. Hamman RF, Mayer EJ, Moo-Young GA, Hildebrandt W, Marshall JA, Baxter J. Prevalence and risk factors of diabetic retinopathy in non-Hispanic whites and Hispanics with NIDDM. San Luis Valley Diabetes Study. Diabetes 1989; 38: 1231-7.

30. Harris Nwanyanwu K, Talwar N, Gardner TW, Wrobel JS, Herman WH, Stein JD. Predicting development of proliferative diabetic retinopathy. Diabetes Care 2013; 36: 1562-8.