Prevalence and Associated Factors of Diabetic Retinopathy in Rural Korea: The Chungju Metabolic Disease Cohort Study

Ji-Hyun Kim¹, Hyuk-Sang Kwon¹, Yong-Moon Park², Jin-Hee Lee¹, Man-Soo Kim¹, Kun-Ho Yoon¹, Won Chul Lee², Bong-Yun Cha¹ and Ho-Young Son¹

Departments of ¹Internal Medicine, ²Preventive Medicine and ³Ophthalmology, College of Medicine, The Catholic University of Korea, Seoul; ⁴The Catholic Institute of Ubiquitous Healthcare, Seoul, Korea

INTRODUCTION

The number of people with type 2 diabetes mellitus has increased worldwide (1). This epidemic is pronounced in the Asia-Pacific region, and the increase in type 2 diabetes has been more rapid in Asia than in other regions (2). Data showed that during the last 25 yr, the prevalence of diabetes has doubled in the USA and multiplied by three to five times in India, Indonesia, China, Korea, and Thailand (3). Consequently, diabetic retinopathy, the major ocular complication of diabetes, is the leading cause of visual impairment and blindness in working-age people in the Asia-Pacific region (4). Its contribution to vision impairment in patients with diabetes is of great interest. Because microvascular complications are directly related to the duration of diabetes mellitus, early detection of retinopathy is an important preventive strategy (5). Furthermore, type 2 diabetes usually has an asymptomatic phase between the actual onset of diabetic hyperglycemia and clinical diagnosis; diabetic retinopathy may be present at the time of clinical diagnosis (6). Diabetic retinopathy can be treated effectively if it is detected early, and blindness can be prevented in the majority of cases by good glycemic control and timely laser treatment (7). Therefore, a correct, reliable evaluation of the population prevalence and severity of diabetic retinopathy is important for public health planning and treatment services in the individuals with type 2 diabetes.

The prevalence of diabetic retinopathy varies widely among populations and the rate has increased considerably worldwide in recent decades (8-11). However, a few Asian group studies have been conducted, but a paucity of recent population-based data exist on the prevalence of diabetes-related eye diseases in Asian countries such as Korea, which in fact, has rapidly increased in the number of individuals with diabetes (3). The current study determined the prevalence and associated factors of diabetic retinopathy in rural Korean patients with type 2 diabetes. Particular emphasis was placed on the group of patients already affected by retinopathy shortly after the onset of diabetes.

MATERIALS AND METHODS

This study was based on the Chungju Metabolic Disease Cohort Study (CMC study), a community-based ongoing prospective cohort study of rural Korean adults, aged 40 yr or older living in Chungju, South Korea, since 2003. At baseline, subjects were selected and investigated using random cluster sampling be-
between 2003 and 2006 after being stratified by the residential areas of 13 health subcenters and 16 community health clinics on the rural area of Chungju city. Details of recruitment methods have been described previously (12). The eligibility criteria included age of 40 yr or older, sufficient mental and physical ability to participate.

A population-based, cross sectional diabetic retinopathy survey was conducted from 2005 to 2006. It was based on the data from participants with type 2 diabetes identified in the CMC study between 2003 and 2006. The eligibility criteria included known or newly diagnosed type 2 diabetes, age of 40 yr or older and sufficient mental and physical ability to participate. A total of 1,713 adults with type 2 diabetes were invited to take part in this study, of whom 1,510 participated (88.1%). Among them, 212 individuals with missing value of diabetes related clinical parameters or ophthalmologic test were excluded from the analysis. In total, 1,298 individuals (505 men and 793 women) (75.7%) participated in this diabetic retinopathy survey, of whom 291 patients (116 men and 175 women) were designated as having newly diagnosed type 2 diabetes. Known diabetes was defined as a self-reported history of diabetes and the current use of diabetic medication using the information from participants who had been asked if they had ever been diagnosed with type 2 diabetes at a clinic. For people without a history of diabetes, a fasting plasma glucose (FPG) ≥ 126 mg/dL on two separate occasions comprised the criteria for diagnosis of diabetes, according to the World Health Organization diabetes classification (14). The duration of diabetes from the time of diagnosis was recorded and those who presented within a year of onset were classified as newly diagnosed.

Clinical measurement
The questionnaires were taken and a physical examination was performed by trained investigators using standard protocols. The questionnaires included information about medical history; duration of diabetes; family history; medication; lifestyle factors such as diet, exercise, and smoking; history of cardiovascular disease; diabetic foot; and peripheral neuropathy. The questionnaire used in this study simply included the presence of diabetic neuropathy symptom, and the history of diagnosis or current treatment of diabetic neuropathy in clinics or hospital. The symptom modalities for diabetic neuropathy were classified into burning, numbness, tingling, fatigue, aching or cramping in the feet, calves or elsewhere. From the results of questionnaire, the patients with those symptoms or history of diagnosis and/or treatment were defined to have diabetic peripheral neuropathy.

Postprandial glucose data was obtained from self measured blood glucose levels of study subject. They were required self measurement of capillary postprandial glucose for a week before their visit for study. Postprandial glucose measurements were made 2 hr after the beginning of the meal, generally peak levels in patients with diabetes. They checked more than 2 times of postprandial glucose levels daily for a week. And investigators confirmed that levels by record of the subjects, and individuals without values more than 180 mg/dL totally were classified as a group of postprandial glucose ≤ 180 mg/dL and the others as a group of > 180 mg/dL. Authors assessed that levels of postprandial glucose levels of 180 mg/dL was according to the glycemic recommendations for peak postprandial capillary plasma glucose of the American Diabetes Association guideline.

A physical examination was performed by measuring height, weight, and waist and hip circumference according to the standardized method. Body mass index was calculated as weight (kg)/height (m)². Blood pressure was measured after participants had been seated for at least 5 min using a standard mercury Baumomanometer according to the World Health Organization-International Society of Hypertension guidelines (15). The blood pressure on the right upper arm was measured twice, 2 min apart and if the difference in diastolic blood pressure was less than 5 mmHg, the average of two measurements was obtained.

Laboratory test
All blood samples were drawn after an overnight 12-hr fast and centrifuged to obtain serum within 30 min. After being frozen, the samples were shipped on dry ice to the Seoul St. Mary’s Hospital and stored at -70°C until analysis. All blood analyses were performed in a central laboratory (Samkwang Medical Laboratories, Seoul, Korea) for accuracy and consistency. Plasma glucose concentrations were assessed using a glucose hexokinase method. HbA1c (Hemoglobin A1c) was determined by ion exchange high-performance liquid chromatography (Variant II turbo; Bio-Rad Laboratories, Inc., Hercules, CA, USA). Total serum cholesterol and triglycerides were measured using an enzymatic calorimetric test, high density lipoprotein (HDL) cholesterol was measured by a selective inhibition method, and low density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula (16).

Diabetic retinopathy
The presence of retinopathy was assessed by one experienced ophthalmologist with indirect funduscopy after dilating the pupils. Diabetic retinopathy was clinically graded according to the new diabetic retinopathy disease severity scale (17). The results were defined as no apparent retinopathy, mild, moderate or severe non-proliferative diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR). The ophthalmologist described each category of the funduscopy findings as follows: 1) No apparent retinopathy, no abnormalities; 2) mild NPDR, more than just microaneurysms but less than severe nonproliferative diabetic retinopathy; 4) severe NPDR, any of the following: more than 20 intraretinal hemorrhages in each of 4 quadrants; definite venous bea-
Diabetic Retinopathy Prevalence and Associated Factors

Kim J-H, et al.

RESULTS

The overall prevalence of diabetic retinopathy was 18.0% in rural Korean patients with type 2 diabetes, including NPDR in 16.7% and PDR in 1.3%. The prevalence of mild, moderate, and severe NPDR was 9.7%, 3.2%, and 3.7%, respectively (Table 1). Among the 291 newly diagnosed patients, 6.2% had a diabetic retinopathy already present and 2.4% suffered from vision threatening form, 1.7% of severe NPDR and 0.7% of PDR.

The characteristics of the study population are summarized in Table 2. No difference in the mean age was observed between the retinopathy and no-retinopathy groups, but significant differences were recorded for diastolic blood pressure and HbA1c between the groups. The mean HbA1c of the patients without retinopathy was 6.8%, which was much less than the 7.5% among patients with retinopathy.

When all patients were considered together, the relative frequency of diabetes related parameters differed according to the presence of diabetic retinopathy (Table 3). The clinical parameters associated with the incidence of retinopathy in the univariate analysis included the duration of diabetes, postprandial plasma glucose, and presence of diabetic foot. A longer duration of diabetes and higher postprandial blood glucose levels above 180 mg/dL indicated higher incidences of diabetic retinopathy.

Table 3. Relative frequency of diabetes related parameters according to presence of diabetic retinopathy

| Parameters                  | No Retinopathy (n = 1,065) | Retinopathy (n = 233) | P value |
|-----------------------------|-----------------------------|-----------------------|---------|
| Duration of diabetes (yr)   |                             |                       |         |
| < 1                         | 208 (19.5)                  | 10 (4.3)              | < 0.001 |
| 1-5                         | 451 (42.4)                  | 47 (20.2)             |         |
| 5-10                        | 222 (20.8)                  | 54 (23.2)             |         |
| > 10                        | 184 (17.3)                  | 122 (52.3)            |         |
| Postprandial glucose        |                             |                       | < 0.001 |
| ≤ 180 mg/dL                 | 513 (48.2)                  | 43 (18.5)             |         |
| > 180 mg/dL                 | 552 (51.8)                  | 190 (81.5)            |         |
| Peripheral neuropathy       | 494 (46.4)                  | 126 (54.1)            | 0.104   |
| Diabetic foot               | 29 (2.7)                    | 19 (8.2)              | 0.002   |
| Treatment of diabetes       |                             |                       | 0.101   |
| Insulin                     | 293 (27.5)                  | 50 (21.5)             |         |
| Oral medication             | 724 (68.0)                  | 168 (72.1)            |         |
| Diet and exercise           | 48 (4.5)                    | 15 (6.4)              |         |
| Coronary artery disease     | 165 (15.5)                  | 46 (19.7)             | 0.303   |

Data are presented as n (%).
in patients with type 2 diabetes. A tendency for a history of diabetic foot was observed in the retinopathy group.

In logistic regression model, diabetic retinopathy was significantly associated with the duration of diabetes, postprandial glucose level and HbA1c. The diabetic retinopathy was increased with the long duration of diabetes mellitus (5-10 yr: OR = 5.19; > 10 yr: OR = 10.03, < 1 yr as a reference), and was 2.5-fold greater in patients with postprandial blood glucose levels exceeding 180 mg/dL compared to that of patients with postprandial blood glucose levels below 180 mg/dL with significance. For every 1% elevation of HbA1c, the risk for diabetic retinopathy increased by a factor of 1.34 (95% CI: 1.545-1.980) (Table 4).

**DISCUSSION**

This study showed that diabetic retinopathy is a common complication among rural Korean patients with type 2 diabetes, and many patients were threatened by visual impairment and required laser treatment. The overall prevalence of retinopathy of 18.0% in our study was less than the 34% to 48% reported in previous hospital-based studies conducted on Korean patients (18-20). Proliferative retinopathy of 1.3% was also significantly less prevalent than that reported previously (3.8% to 19.9%). A recent nationwide survey from 13 tertiary hospitals in Korea reported a 38.3% prevalence of diabetic retinopathy (21). However, community-based studies assessing diabetic retinopathy are very limited in Korea. As expected, the prevalence of diabetic retinopathy was lower among those who were examined in the population-based screening compared to those in the diabetic clinics.

As diabetes is highly prevalent and has increased more rapidly in the Asia-Pacific region (2), diabetic retinopathy is the leading cause of visual impairment and blindness in this region (4). Especially in developing Asian countries, the lack of health care facilities for diabetes management remains a serious public health problem. Consequently, the burden imposed by delayed diagnosis of diabetes and its complications could be more common and massive than in developed countries. Therefore, understanding the actual prevalence and progression of diabetic retinopathy is very important for Asian people and worldwide health care planning. In Asian population-based studies conducted prior to 2000, the prevalence of diabetic retinopathy was and 45.2% in Taiwan (22) and 27.3% in Chinese hospital (23). Our result of 18% was lower than these epidemiologic data and similar to that of a population study examining urban and rural India after 2000, in which the overall prevalence of diabetic retinopathy was 19.2% and 17.6%, respectively (24, 25). The causes of this lower overall prevalence of diabetic retinopathy are likely to include the behavioral and nutritional habits of rural Koreans; typically, they eat vegetable-centered diets and have a relatively higher level of physical activity such as farmwork. In addition, differences in susceptibility to diabetic retinopathy may exist among different ethnic groups.

Notably, the prevalence of diabetic retinopathy in recent Korean and Indian studies was less than that observed in other epidemiologic Asian studies conducted before 2000. Although the rate of type 2 diabetes has increased during the past three decades in Asian countries, the prevalence of diabetic retinopathy has not increased. In the Blue Mountain Eye Study of suburban Australians comparing the age-specific prevalence of diabetic retinopathy over 6 yr, although the prevalence of diabetic retinopathy increased from 29.4% to 33.4%, prevalent diabetic retinopathy had become principally mild and the prevalence of more severe diabetic retinopathy levels had decreased (26). In addition, a recent 21.9% prevalence of diabetic retinopathy in Australian population was similar with the result of our study (27).

Another important fact is that usually, type 2 diabetes has an asymptomatic phase with actual diabetic hyperglycemia before clinical diagnosis. This phase has been estimated to last at least 4-7 yr (6). Therefore, identifying diabetic retinopathy from newly diagnosed diabetes is valuable to the prevention and appropriate treatment of diabetic retinopathy in the early stage. Our study observed 6.2% diabetic retinopathy in newly diagnosed diabetics. Compared to the prevalence rate among Asian populations, this rate was lower than that of 30.5% in the Da Qing Study (28), 28.3% in Taiwan (22) and 21.9% in Hong Kong Chinese (29). Recent population-based data from India were similar to our data (6.35% and 5.1%, respectively) (24, 30). This is likely to have occurred following the introduction of new diagnostic criteria for diabetes, which are now less stringent, a better control of diabetic patients by general practitioners and endocrinologists, and more widespread home glucose monitoring. Nevertheless, note that among the newly diagnosed group of patients, proliferative or severe non-proliferative diabetic retinopathy was already present in 2.4% of subjects in our study and 4.6% in the Indian group (30). An earlier diagnosis and more aggressive control of treatment of diabetic retinopathy may be warranted.

Identification and early treatment have a critical role in diabetic retinopathy because the disease is usually progressive and laser treatment is rarely effective in restoring vision. The recognition of modifiable risk factors that have a large potential for

**Table 4. Multivariate analysis* of the diabetic retinopathy related parameters**

| Parameter                  | Odds ratio | CI (95%)          | P value |
|----------------------------|------------|-------------------|---------|
| Duration of diabetes (yr)  |            |                   |         |
| < 1                        | 1.00       |                   |         |
| 1-5                        | 2.239      | 0.493-10.159      | 0.296   |
| 5-10                       | 5.192      | 1.138-23.684      | 0.033   |
| > 10                       | 10.034     | 2.284-44.075      | 0.002   |
| HbA1c (increase 1%)        | 1.344      | 1.116-1.619       | 0.002   |
| Postprandial glucose (> 180 mg/dL) | 2.496 | 1.340-4.647       | 0.004   |

*Multivariate analysis was performed using a logistic regression model with the forward method. CI, confidence interval.
Diabetic retinopathy: a clinical update. Diabetologia 2002; 45: 1617-34.

5. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. III: prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol 1984; 102: 527-32.

6. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. Diabetes Care 1992; 15: 815-9.

7. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-53.

8. Looker HC, Krakoff J, Knowler WC, Bennett PH, Klein R, Hanson RL. Longitudinal studies of incidence and progression of diabetic retinopathy assessed by retinal photography in pima indians. Diabetes Care 2003; 26: 320-6.

9. Leske MC, Wu SY, Hennis A, Nemesure B, Hyman L, Schachat A. Incidence of diabetic retinopathy in the Barbados Eye Studies. Ophthalmology 2003; 110: 941-7.

10. McCarty DJ, Fu CL, Harper CA, Taylor HR, McCarty CA. Five-year incidence of diabetic retinopathy in the Melbourne visual impairment project. Clin Experiment Ophthalmol 2003; 31: 397-402.

11. van Leiden HA, Dekker JM, Moll AC, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD, Polak BC. Risk factors for incident retinopathy in a diabetic and nondiabetic population: the Hoorn study. Arch Ophthalmol 2003; 121: 245-51.

12. Kwon HS, Park YM, Lee HJ, Lee JH, Choi YH, Ko SH, Lee JM, Kim SR, Kang SY, Lee WC, Ahn MS, Noh JH, Kang JM, Kim DS, Yoon KH, Cha BY, Lee KW, Kang SK, Son HY. Prevalence and clinical characteristics of the metabolic syndrome in middle-aged Korean adults. Korean J Intern Med 2005; 20: 310-6.

13. World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 52nd WMA General Assembly. Edinburgh: 2000.

14. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications part 1: diagnosis and classification of diabetes mellitus. World Health Organization, 1999.

15. Chalmers I, MacMahon S, Mancia G, Whithworth J, Beilin L, Hansson L, Neal B, Rodgers A, Ni Mhurchu C, Clark T. 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension. Guidelines sub-committee of the World Health Organization. Clin Exp Hypertens 1999; 21: 1009-60.

16. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18: 499-502.
17. Wilkinson CP, Ferris FL 3rd, Klein RE, Lee PP, Agardh CD, Davis M, Dills D, Kampaik A, Paranajsegaram R, Verdaguer JT; Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003; 110: 1677-82.

18. Lee HC, Yang JY, Lim SK, Hong CS, Huh KB, Lee SY. A prospective study of diabetic complications. J Korean Diabetes Assoc 1984; 8: 47-53.

19. Nam JH, Lee SH, Lee HJ, Han JH, Ha SW, Kim BW. The prevalence of chronic complications in non-insulin dependent diabetic patients. J Korean Diabetes Assoc 1999; 23: 702-14.

20. Park JY, Kim SW, Cho GY, Lee MH, Je SI, Lee KJ, Kim GS. The prevalence of micro- and macrovascular complications of Korean NIDDM patients. J Korean Diabetes Assoc 1993; 17: 377-85.

21. Lim S, Kim DJ, Jeong IK, Son HS, Chung CH, Koh G, Lee DH, Won KC, Park JH, Park TS, Ahn J, Kim J, Park KG, Ko SH, Ahn YB, Lee I. A nationwide survey about the current status of glycemic control and complications in diabetic patients in 2006: The Committee of the Korean Diabetes Association on the Epidemiology of Diabetes Mellitus. Korean Diabetes J 2009; 33: 48-57.

22. Chang C, Lu F, Yang YC, Wu JS, Wu TJ, Chen MS, Chuang LM, Tai TY. Epidemiologic study of type 2 diabetes in Taiwan. Diabetes Res Clin Pract 2000; 50(Suppl 2): S49-59.

23. Liu DP, Molyneaux L, Chua E, Wang YZ, Wu CR, Jing H, Hu LN, Liu YJ, Xu ZR, Yue DK. Retinopathy in a Chinese population with type 2 diabetes: factors affecting the presence of this complication at diagnosis of diabetes. Diabetes Res Clin Pract 2002; 56: 125-31.

24. 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. J. Invest Ophthalmod Vis Sci 2005; 46: 2328-33.

25. Rani PK, Raman R, Chandrakanant A, Pal SS, Perumal GM, Sharma T. Risk factors for diabetic retinopathy in self-reported rural population with diabetes. J Postgrad Med 2009; 55: 92-6.

26. Cugati S, Killey A, Mitchell P, Wang JJ. Temporal trends in the age-specific prevalence of diabetes and diabetic retinopathy in older persons: population-based survey findings. Diabetes Res Clin Pract 2006; 74: 301-8.

27. Tapp RJ, Shaw JE, Harper CA, de Courten MP, Balkau B, McCarty DJ, Taylor HR, Welborn TA, Zimmet PZ; AusDiab Study Group. The prevalence of and factors associated with diabetic retinopathy in the Australian population. Diabetes Care 2003; 26: 1731-7.

28. Hu YH, Pan XR, Liu PA, Li GW, Howard BV, Bennett PH. Coronary heart disease and diabetic retinopathy in newly diagnosed diabetes in Da Qing, China: the Da Qing IGT and Diabetes Study. Acta Diabetol 1991; 28: 169-73.

29. Wang WQ, Ip TP, Lam KS. Changing prevalence of retinopathy in newly diagnosed non-insulin dependent diabetes mellitus patients in Hong Kong. Diabetes Res Clin Pract 1998; 39: 185-91.

30. Agarwal S, Raman R, Kumari BP, Deshmukh H, Paul PG, Gnanamoorthy P, Kumaramanickavel G, Sharma T. Diabetic retinopathy in type II diabetes detected by targeted screening versus newly diagnosed in general practice. Ann Acad Med Singapore 2006; 35: 531-5.

AUTHOR SUMMARY

Prevalence and Associated factors of Diabetic Retinopathy in Rural Korea: The Chungju Metabolic Disease Cohort Study

Ji-Hyun Kim, Hyuk-Sang Kwon, Yong-Moon Park, Jin-Hee Lee, Man-Soo Kim, Kun-Ho Yoon, Won Chul Lee, Bong-Yun Cha and Ho-Young Son

Diabetic retinopathy is the leading cause of blindness in working-age people in the Asia-Pacific region. According to our present study, in 40 ≥ rural Korean patients with type 2 diabetes, the overall prevalence of diabetic retinopathy was 18% and proliferative or severe non-proliferative form was found in 5.0% of the study subjects. Factors associated with retinopathy included duration of diabetes, hemoglobin A1c, and postprandial blood glucose levels. The number of patients with proliferative or severe non-proliferative diabetic retinopathy was comparable with the overall rate in Asian countries, and identified more frequently at the time of diagnosis. More aggressive identification and early treatment are necessary for diabetic retinopathy.