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

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This study was aimed to investigate the prevalence of diabetic retinopathy and its associated factors in rural Korean patients with type 2 diabetes. A population-based, cross-sectional diabetic retinopathy survey was conducted from 2005 to 2006 in 1,298 eligible participants aged over 40 yr with type 2 diabetes identified in a rural area of Chungju, Korea. Diabetic retinopathy was diagnosed by a practicing ophthalmologist using funduscopy. The overall prevalence of diabetic retinopathy in the population was 18% and proliferative or severe non-proliferative form was found in 5.0% of the study subjects. The prevalence of retinopathy was 6.2% among those with newly diagnosed type 2 diabetes and 2.4% of them had a proliferative or severe non-proliferative diabetic retinopathy. The odds ratio of diabetic retinopathy increased with the duration of diabetes mellitus (5-10 yr: 5.2- fold; > 10 yr: 10-fold), postprandial glucose levels (> 180 mg/dL: 2.5-fold), and HbA1c levels (every 1% elevation: 1.34-fold). The overall prevalence of diabetic retinopathy in rural Korean patients was similar to or less than that of other Asian group studies. However, the number of patients with proliferative or severe non-proliferative diabetic retinopathy was still high and identified more frequently at the time of diagnosis. This emphasizes that regular screening for diabetic retinopathy and more aggressive management of glycemia can reduce the number of people who develop diabetic retinopathy.

Key Words: Diabetic Retinopathy; Prevalence; Risk Factors

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 a cohort of rural Korean type 2 diabetes patients. 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-

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tween 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 funduscopic findings as follows: 1) No apparent retinopathy, no abnormalities; 2) mild NPDR, microaneury only; 3) moderate 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 bead-

ing in 2 quadrants; prominent intraretinal microvascular abnormalities in 1 quadrant and no signs of proliferative reinopathy; and 5) PDR, one or more of the following: neovascularization, vitreous/preretinal hemorrhage.

Analysis and statistics

First, the prevalence of diabetic retinopathy was analyzed in our study population. And then, the relationship between diabetic retinopathy and various parameters was assessed to detect risk factors. The results are expressed as the mean ± SD. For the univariate analysis, an independent t-test was used to compare continuous variables, and cross-tab analysis with the chi-squared test or Fisher's exact test was used to compare proportions among groups. To identify correlates of retinal disease progression, a multivariate logistic regression analysis was conducted using the identified significant variables for all cases with complete data. The odds ratios and 95% confidence limits were calculated to determine the association between diabetic retinopathy and the various parameters. The level of significance was considered to be $P < 0.05$. The data were analyzed using SPSS version 11.0 for Windows (SPSS Inc., Chicago, IL, USA).

Table 1. Prevalence of diabetic retinopathy among study subjects

	Total number of diabetes	Newly diagnosed diabetes
n	1,298	291
Age (yr)	67.7 ± 8.8	65.9 ± 9.4
Sex (M/F)	505/793	116/175
No retinopathy	1,065 (82.0)	273 (93.8)
Retinopathy		
Mild NPDR	126 (9.7)	7 (2.4)
Mod NPDR	42 (3.2)	4 (1.4)
Severe NPDR	48 (3.7)	5 (1.7)
PDR	17 (1.3)	2 (0.7)

Data are presented as the mean ± SD or n (%). NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 2. Baseline clinical characteristics according to the presence of retinopathy

	No Retinopathy (n = 1,065)	Retinopathy (n = 233)	*P* value
Age (yr)	67.7 ± 8.9	67.6 ± 8.5	0.755
BMI (kg/m^2)	24.5 ± 3.1	24.6 ± 2.5	0.949
Systolic blood pressure (mmHg)	133.2 ± 18.8	132.1 ± 20.3	0.327
Diastolic blood pressure (mmHg)	81.2 ± 10.5	79.2 ± 12.0	0.022
Fasting blood glucose (mg/dL)	104.5 ± 25.6	100.6 ± 14.3	0.938
HbA1c (%)	6.8 ± 1.3	7.5 ± 1.7	0.000
Total cholesterol (mg/dL)	201.5 ± 37.4	222.8 ± 41.7	0.076
HDL-cholesterol (mg/dL)	47.1 ± 8.5	49.6 ± 10.1	0.596
Triglycerides (mg/dL)	166.1 ± 86.0	178.4 ± 98.9	0.681
LDL-cholesterol (mg/dL)	119.6 ± 32.7	133.5 ± 40.4	0.117
Hypertension	560 (52.6)	110 (47.2)	0.167
Family history of diabetes	172 (16.2)	41 (17.6)	0.589
Coronary artery disease	165 (15.5)	46 (19.7)	0.303
Smoking	234 (22.0)	50 (21.5)	0.884
Exercise regularly	315 (29.6)	83 (35.6)	0.100
Diet control	503 (47.2)	111 (47.6)	0.904

Data are presented as the mean ± SD or n(%). BMI, body mass index; HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol; Low-density lipoprotein cholesterol.

Ethics statement

This study was performed in accordance with the revised Declaration of Helsinki guidelines for biomedical research involving human subjects (13) and was approved by the institutional review board of the Catholic University of Korea and informed consent was obtained from all participants.

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)			< 0.001
< 1	208 (19.5)	10 (4.3)	
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 (%).

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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.

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 diabetes. 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

affecting health outcomes is very important. The results of prospective, population-based studies have strongly and consistently implicated a longer duration of diabetes and poor glycemic control with diabetic retinopathy (5, 7, 8). Large randomized clinical trial has reported that intensive glycemic control results in clinically significant reductions in the incidence and progression of retinopathy and loss of vision (8).

In this study, the duration of diabetes, HbA1c, and postprandial glucose levels were associated with diabetic retinopathy in the multivariate analysis. In particular, the duration of diabetes showed a significant association with diabetic retinopathy. This concurs with findings that the duration of diabetes is a key risk factor for diabetic retinopathy (5, 7, 8). The duration of diabetes is considered to be a marker for long-term exposure to hyperglycemia. Other studies have consistently identified glycemic control as an independent risk factor for retinopathy (26, 27). In this study population, HbA1c and postprandial glucose levels were other factors independently associated with diabetic retinopathy. Glycemic control was good with a mean HbA1c of 7.5% and a fasting blood glucose level of 100.6 mg/dL in the retinopathy group; therefore, the postprandial glucose level can be considered to be a determinant of glycemic control.

Although the strength of our study is that it was the first population-based study to assess the prevalence of diabetic retinopathy in Korea, this study has some limitations. First, because it was a cross-sectional study, causality was not evaluated. Second, there is a difference between prevalence in rural area and prevalence in big cities in Korea. Therefore, the findings of this study can not be regarded as a nationally representative data. Because diabetic retinopathy is a progressive disorder, a one-time cross-sectional screening would not be sufficient to evaluate and alleviate the burden of diabetic retinopathy. Regularly repeated surveys for the prevalence of diabetic retinopathy and prospective study of progression need to be performed to reduce the visual morbidity of type 2 diabetes. Furthermore, one should not neglect the detection and treatment of diabetic retinopathy just because risk-factor control is expected to minimize its prevalence. An earlier diagnosis and more aggressive control of blood glucose can decrease the duration-adjusted prevalence of retinopathy and sight-threatening complications.

In conclusion, the present study suggests that the prevalence of diabetic retinopathy in rural Korea is lower than that reported in other previous Asian groups. Nevertheless, proliferative or severe non-proliferative diabetic retinopathy still exists and progresses in many patients with diabetes due to increased diabetes burden, and it remains a public health and economic burden in Korea. This emphasizes that regular screening for diabetic retinopathy and more aggressive management of glycemia can reduce the number of people who develop diabetic retinopathy.

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AUTHOR SUMMARY

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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.