The Relationship Between Diabetic Retinopathy and Diabetic Nephropathy in a Population-Based Study in Korea (KNHANES V-2, 3)

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Purpose. To determine the risk factors for and relationship between diabetic retinopathy (DR) and diabetic nephropathy (DN), including microalbuminuria and overt nephropathy, in a population-based study of diabetes mellitus (DM) patients in Korea.

Methods. This was a population-based, cross-sectional study. From the fifth (2011, 2012) Korea National Health and Nutrition Examination Survey (KNHANES), 971 participants with type 2 DM were included. The prevalence of DR and DN was determined. Multivariate logistic regression was performed to determine risk factors, including DR, associated with DN in the Korean population.

Results. In DM patients, we observed a prevalence of 20.0% for any DR and 3.8% for proliferative diabetic retinopathy (PDR). Microalbuminuria prevalence was 19.3% and overt nephropathy prevalence was 5.5%. The risk factors of microalbuminuria were presence of hypertension; higher systolic blood pressure, serum hemoglobin A1c (HbA1c), and serum blood urea nitrogen level; as well as the presence of PDR. The risk factors of overt nephropathy were long duration of DM; high levels of HbA1c, systolic blood pressure, total cholesterol, and serum creatinine; as well as the presence of DR

Conclusions. Proliferative diabetic retinopathy is associated with microalbuminuria and DR is associated with overt nephropathy in Korean DM patients. Our findings suggest that when an ophthalmologist finds the presence of DR or PDR, timely evaluation of the patient's renal status should be recommended.

Keywords: diabetic nephropathy, diabetic retinopathy, epidemiological study, KNHANES, microalbuminuria, overt nephropathy

Recent epidemiological studies have shown a significant rise in the prevalence of diabetes mellitus (DM) worldwide.[1,2] The prevalence of DM in Korea also has increased 6- to 7-fold, from 1.5% to 9.9%, over the past 40 years.[3,4] This global increase in the prevalence of DM will inevitably lead to increases in the prevalence of diabetic microvascular (predominantly retinopathy, nephropathy, and neuropathy) and macrovascular complications. These complications will be significant burdens for these individuals and on our health care systems.[5,6]

The retina and the kidney complications of DM both result from damage to small vessels in these organs. These diabetic microvascular complications may have devastating consequences, including blindness and end-stage renal disease. Some authors have identified associations between the complications themselves, and one complication can serve as a risk factor for another. Recently, studies have shown that the presence of diabetic retinopathy (DR) itself may leave patients at risk for diabetic nephropathy (DN).[7–10] However, studies about the relationship between DR and DN are limited for Korean patients and, furthermore, population-based studies of this association have not been performed yet in Korea. It is possible that ethnic/racial differences may lead to varying susceptibilities to diabetic microvascular complications.

We hypothesized that the presence of DR could suggest there is concomitant injury to renal small vessels and an increased risk of DN in the Korean population. To test this, we examined which risk factors, including DR, were associated with DN in the Korea National Health and Nutrition Examination Survey (KNHANSE V-2, 3) data.

Subjects and Methods

This study was reviewed and approved by the institutional review board of the Korean Centers for Disease Control and Prevention (Institutional Review Board Number: 2011-02CON-06-C, 2012-01EXP-01-2C), and all participants provided written informed consent.

Design and Study Population

The KNHANES is a nationwide population-based survey of the health and nutritional status of noninstitutionalized Korean

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people. It began in 1998, and surveys were conducted in 1998, 2001, 2005, 2007 to 2009, and 2010 to 2012. A stratified multistage clustered probability design was used to select a representative sample of civilian, noninstitutionalized Korean adults. The KNHANES consisted of three parts: (1) the Health Interview Survey, (2) the Health Examination Survey, and (3) the Nutritional Survey. The Health Interview Survey was administered to all study participants, but the Health Examination Survey and Nutritional Survey were administered to approximately a third of the participants randomly selected from the participants of the Health Interview Survey. The subjects included in our analysis were 30 years and older; had participated in the 2011, 2012 KNHANES V-2, 3 surveys; and completed the Health Interview Survey and Health Examination Survey. Urine albumin level was not measured in KNHANES V-1 (2010), so we used only the data from KNHANES V-2, 3. Diabetes mellitus was defined as a previous diagnosis of DM made by a physician, use of insulin or oral hypoglycemic agents, and/or a fasting blood glucose (FBG) of 126 mg/dL or higher. Participants were considered to have type 1 DM if they were younger than 30 years when diagnosed with DM and were receiving insulin therapy. Otherwise, DM was considered type 2 DM. In this study, we included only patients with type 2 DM.

Risk Factor Measurement

Possible risk factors for DN, including sex, age, hypertension (presence, duration, systolic blood pressure, diastolic blood pressure), the duration of DM, FBG, HbA1c, lipid profile (triglyceride, total cholesterol, low density lipoprotein [LDL] cholesterol), blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), urine albumin-creatinine ratio, history of smoking (ever smoker/current smoker), and presence of DR, proliferative DR (PDR), and clinically significant macular edema (CSME) were evaluated. From the KNHANES V-2, 3 databases, we collected data regarding various factors obtained through direct interviews using standardized questionnaires.

Blood Pressure and Diabetes Duration. Blood pressure was measured three times on the right arm while the individual was in a seated position after at least 5 minutes of rest using a mercury sphygmomanometer (Baumanometer; W.A. Baum Co., Copiague, NY, USA). The final blood pressure value was obtained by averaging the second and third blood pressure measurements. Subjects were defined as hypertensive if systolic pressure was 140 mm Hg or higher or diastolic pressure was 90 mm Hg or higher, according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).[11]

The duration of DM was estimated through the interviews, and the duration of the newly diagnosed DM discovered via blood sampling as part of the study is regarded as "0."

Biochemical Measurements. Blood samples were collected in the morning after the participant had fasted for at least 8 hours. Fasting blood samples and spot urine samples collected from each participant were processed, refrigerated immediately, and transported in cold storage to the central laboratory (Neodin Medical Institute, Seoul, Korea). All samples were analyzed within 24 hours after transportation.

Ophthalmic Examinations and Grading of DR. Nonmydriatic fundus photography (TRC-NW6S; Topcon, Tokyo, Japan) was performed in all KNHANES participants. In participants with history of DM or a random blood glucose level of 200 mg/dL or higher and/or suspicion of DR on nonmydriatic photography, seven standard field photographs as per the Early Treatment for Diabetic Retinopathy Study (ETDRS) protocol were obtained from each eye after pharmacological pupil dilation.[12,13]

Diabetic retinopathy was identified if any characteristic lesion as defined by the ETDRS severity scale was present: microaneurysms, hemorrhages, hard exudates, cotton wool spots, intraretinal microvascular abnormalities, venous beading, and retinal new vessels. A DR severity score was assigned to each eye according to the modification of the Airlie House Classification system (see Supplementary Material S1).[12–15] The level of retinopathy was graded based on the worse eye. Eyes were graded according to the following criteria: no DR (level 10-13), non-PDR (NPDR) (level 14–51), and PDR (level > 60).[12–15]

Clinically significant macular edema was defined according to ETDRS criteria (see Supplementary Material S2).[16]

Each fundus image was graded twice. Preliminary grading was done onsite by ophthalmologists trained by the National Epidemiologic Survey Committee of the Korean Ophthalmologic Society (KOS). Second, 13 retinal specialists with expertise in the grading of DR performed detailed grading. The retinal specialists resolved any discrepancies between preliminary and detailed grading. The quality of the survey was verified by the Epidemiologic Survey Committee of the KOS. Grading agreement between the preliminary graders and the retinal specialists ranged from 98.2% to 98.4%. Training of participating residents was periodically performed by the National Epidemiologic Survey Committee of the KOS.

Determination of DN and Estimation of GFR

Patients were classified into three renal status groups: microalbuminuria, overt nephropathy, and no-diabetic nephropathy (no-DN). We compared clinical data and ophthalmologic results among the microalbuminuria, overt nephropathy, and no-DN groups. Presence of microalbuminuria was defined as protein excretion of 30 to 300 mg per 24 hours or albumin/creatinine ratio of 30 to 300 μg/mg. Presence of overt nephropathy was defined as protein excretion of more than 300 mg per 24 hours or albumin/creatinine ratio greater than 300 μg/mg. Presence of overt DN is defined as microalbuminuria or overt nephropathy, in the absence of other renal disease.[17]

The level of kidney function was ascertained by using an abbreviated equation developed using data from the Modification of Diet in Renal Disease study[18] to estimate the GFR as follows: $\text{eGFR} = 186.3 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times$ (0.742 for women). We defined chronic kidney disease (CKD) as eGFR less than 60 mL/min/1.73m^2.[19,20]

Statistical Analysis

Descriptive statistical methods were used to delineate the basic characteristics of the study population: number and percentages were reported for each variable. Results were expressed as mean $\pm$ SD, and a P value less than 0.05 was considered to indicate statistical significance. Differences between the groups were analyzed using the independent-sample t-test for continuous variables, such as age or FBG. For the categorical variables, such as presence of DR or sex, we used the χ^2 test.

A two-step, multidimensional approach was used to identify the factors associated with DN. First, to identify factors associated with DN occurrence, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using univariate logistic regression analysis. Second, multivariate logistic regression was used to determine independent risk factors. All the risk factors that were identified as affecting DN occurrence by univariate analysis ($P < 0.1$) were included in the multivariate analysis to determine which factors were most associated with DN. For the relationship between DR and CKD, we used univariate logistic regression. All statistical tests were

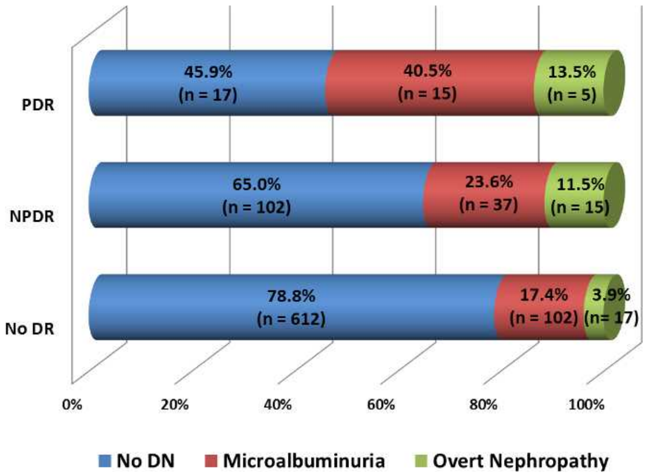

Figure. Distribution of stages of nephropathy (DN) among patients with different degrees of DR.

performed using the PASW Statistics 18 (SPSS, Chicago, IL, USA).

Results

Prevalence of DR and DN in KNHANES V-2, 3

In the 971 DM patients who met inclusion criteria, we observed a prevalence of 20.0% ($n = 194$) for DR and 3.8% ($n = 37$) for PDR. Microalbuminuria prevalence was 19.3% ($n = 187$) and overt nephropathy prevalence was 5.5% ($n = 53$).

The Figure shows the distribution of degrees of DN among different DR grades. Patients with both PDR and NPDR were more likely to have DN than patients without DR.

Table 1 provides the comparison of characteristics between the no-DN group and the microalbuminuria and overt nephropathy groups. Patients with microalbuminuria were more likely to have hypertension (73.0% in the microalbuminuria versus 57.7% in the no-DN group, $P = 0.002$), higher systolic blood pressure (132.7 ± 17.8 mm Hg vs. 126.6 ± 16.0 mm Hg, $P < 0.001$), and higher BUN levels (17.2 ± 5.5 mg/dL vs. 15.8 ± 4.5 mg/dL, $P = 0.011$) than the patients without DN. Patients with microalbuminuria were more likely to be older (64.51 ± 11.47 vs. 61.91 ± 10.97 years, $P = 0.004$), have longer duration of DM (8.2 ± 8.4 vs. 6.2 ± 7.5 years, $P = 0.003$), and higher HbA1c levels (7.56% ± 1.50% vs. 7.32% ± 1.39%, $P = 0.041$) than the patients without DN. Patients with microalbuminuria were more likely to have DR (27.8% vs. 16.3%, $P < 0.001$) and PDR (8.0% vs. 2.3%, $P < 0.001$) than the patients without DN. Other characteristics showed no significant differences.

Most of the characteristics that showed significant difference between the no-DN group and the microalbuminuria group also revealed significant difference between the no-DN group and the overt nephropathy group (Table 1). Additionally, patients with overt nephropathy were more likely to have higher levels of FBG (153.1 ± 54.3 vs. 139.5 ± 41.1 mg/dL, $P = 0.023$), higher total cholesterol levels (200.4 ± 41.1 vs. 185.2 ± 42.1 mg/dL, $P = 0.011$), and higher serum creatinine levels (1.07 ± 0.45 vs. 0.86 ± 0.21 mg/dL, $P = 0.002$) than patients without DN. Patients with overt nephropathy were more likely to be current smokers (35.8% vs. 20.7%, $P = 0.010$) than the patients without DN. Other characteristics showed no significant differences.

Risk Factors Associated With Microalbuminuria in Korean DM Patients

Table 2 shows the risk factors for microalbuminuria determined by multivariate logistic regression. The presence of

Table 1. Comparison of Characteristics Among No-DN, MA, and ON Groups in DM Patients

	No-DN, n = 731	MA, n = 187	ON, n = 53	*P* Value (1)	*P* Value (2)
Men, %	51.3	48.7	60.4	0.244	0.202
Age, y	61.91 (10.97)	64.51 (11.47)	64.74 (10.92)	0.004	0.070
HTN, %	57.7	73.0	79.2	<0.001	0.002
Duration of HTN, y	8.00 (7.90)	8.53 (8.10)	8.71 (8.74)	0.506	0.582
SBP, mm Hg	126.6 (16.0)	132.7 (17.8)	137.3 (21.4)	<0.001	0.001
DBP, mm Hg	75.7 (9.9)	76.3 (13.2)	76.6 (11.7)	0.571	0.605
Duration of DM, y	6.2 (7.5)	8.2 (8.4)	10.3 (9.1)	0.003	0.002
FBG, mg/dL	139.5 (41.1)	144.8 (43.6)	153.1 (54.3)	0.116	0.023
HbA1c, %	7.32 (1.39)	7.56 (1.50)	8.04 (1.68)	0.041	0.004
Triglycerides, mg/dL	169.6 (143.6)	180.3 (127.9)	217.3 (174.1)	0.353	0.056
Total cholesterol, mg/dL	185.2 (42.1)	186.3 (37.8)	200.4 (41.1)	0.752	0.011
LDL cholesterol, mg/dL	111.4 (38.6)	105.2 (33.9)	126.5 (32.1)	0.292	0.168
BUN, mg/dL	15.7 (4.4)	17.2 (6.7)	18.8. (6.2)	0.005	0.001
Creatinine, mg/dL	0.86 (0.21)	0.93 (0.45)	1.07 (0.45)	0.069	0.002
eGFR, mL/min/1.73m^2	87.21 (18.33)	83.36 (22.70)	77.02 (26.09)	0.033	0.007
ACR, μg/mg	8.00 (7.37)	86.94 (65.67)	1213.98 (166.75)	<0.001	<0.001
Ever smoker*	48.3	44.4	56.6	0.341	0.242
Current smoker	20.7	18.7	35.8	0.545	0.010
DR, %	16.3	27.8	43.4	<0.001	<0.001
PDR, %	2.3	8.0	9.4	<0.001	0.002
CSME, %	0.5	2.1	1.9	0.059	0.296

Values are expressed as mean (SD) or percentage. ACR, urine albumin creatinine ratio; DBP, diastolic blood pressure; HTN, hypertension; MA, microalbuminuria; ON, overt nephropathy; SBP, systolic blood pressure. (1) Comparison between no-DN and MA groups. (2) Comparison between no-DN and ON groups.

* A person who has smoked ≥100 cigarettes during the course of his or her life.

TABLE 2. Risk Factors Associated With MA in Korean DM Patients

Variable	Univariate OR	Univariate 95% CI	Univariate P Value	Multivariate aOR	Multivariate 95% CI	Multivariate P Value
Men	0.83	0.60–1.14	0.244			
Age, y	1.02	1.01–1.04	0.004	1.01	0.99–1.03	0.318
HTN	1.98	1.39–2.83	<0.001	1.53	1.01–2.32	0.043
Duration of HTN, y	1.01	0.98–1.03	0.505			
SBP, mm Hg	1.02	1.01–1.03	<0.001	1.02	1.01–1.03	<0.001
DBP, mm Hg	1.01	0.99–1.02	0.504			
Duration of DM, y	1.03	1.01–1.05	0.002	1.01	0.99–1.03	0.453
FBG, mg/dL	1.00	1.00–1.01	0.117			
HbA1c, %	1.12	1.00–1.24	0.042	1.18	1.05–1.32	0.006
Triglycerides, mg/dL	1.00	1.00–1.00	0.359			
Total cholesterol, mg/dL	1.00	1.00–1.01	0.751			
LDL cholesterol, mg/dL	1.00	0.99–1.00	0.291			
BUN, mg/dL	1.06	1.02–1.09	0.001	1.04	1.01–1.08	0.013
Creatinine, mg/dL	2.06	1.13–3.76	0.018	1.55	0.49–4.85	0.455
eGFR, mL/min/1.73m^2	0.99	0.98–1.00	0.016	1.01	0.99–1.02	0.453
Ever smoker	0.86	0.62–1.18	0.341			
Current smoker	0.88	0.59–1.33	0.545			
DR	1.98	1.36–2.88	<0.001	1.18	0.74–1.88	0.488
PDR	3.66	1.79–7.48	<0.001	3.03	1.44–6.40	0.004
CSME	3.97	0.98–16.04	0.053	2.61	0.55–12.29	0.225

hypertension (adjusted OR [aOR] 1.53; 95% CI 1.01–2.32), the presence of systolic arterial hypertension (aOR 1.02; 95% CI 1.01–1.03), high HbA1c (aOR 1.18; 95% CI 1.05–1.32), high serum BUN level (aOR 1.04, 95% CI 1.01–1.08), and the presence of PDR (aOR 3.03, 95% CI 1.44–6.40) were significantly associated with microalbuminuria.

Risk Factors Associated With Overt Nephropathy in Korean DM Patients

Table 3 shows the risk factors for overt nephropathy determined by multiple logistic regression analysis. Presence of systolic arterial hypertension (aOR 1.03, 95% CI 1.01–1.05), long duration of DM (aOR 1.04, 95% CI 1.00–1.08), high HbA1c (aOR 1.30, 95% CI 1.07–1.57), high total cholesterol level (aOR 1.01, 95% CI 1.00–1.02), high serum creatinine level (aOR 8.54, 95% CI 3.13–23.34), and the presence of DR (aOR 2.11, 95% CI 1.04–4.26) were significantly associated with overt nephropathy.

Risk for CKD in Patients With Presence of DR and PDR Relative to Those With No-DR

We also investigated DR and PDR as risk factors for CKD in DM patients. Diabetic retinopathy and PDR are associated with CKD in the microalbuminuria group (univariate logistic

TABLE 3. Risk Factors Associated With ON in Korean DM Patients

Variable	Univariate OR	Univariate 95% CI	Univariate P Value	Multivariate aOR	Multivariate 95% CI	Multivariate P Value
Men	1.45	0.82–2.56	0.204			
Age, y	1.03	1.00–1.05	0.071	1.01	0.97–1.05	0.576
HTN	2.80	1.42–5.53	0.003	2.24	0.94–5.35	0.070
Duration of HTN, y	1.01	0.97–1.05	0.581			
SBP, mm Hg	1.04	1.02–1.05	<0.001	1.03	1.01–1.05	0.001
DBP, mm Hg	1.01	0.98–1.04	0.548			
Duration of DM, y	1.06	1.03–1.09	<0.001	1.04	1.00–1.08	0.029
FBG, mg/dL	1.01	1.00–1.01	0.025	1.00	0.99–1.01	0.804
HbA1c, %	1.31	1.12–1.53	0.001	1.30	1.07–1.57	0.007
Triglycerides, mg/dL	1.00	1.00–1.00	0.041	1.00	1.00–1.00	0.177
Total cholesterol, mg/dL	1.01	1.00–1.01	0.012	1.001	1.00–1.02	0.008
LDL cholesterol, mg/dL	1.01	1.00–1.02	0.171			
BUN, mg/dL	1.12	1.07–1.18	<0.001	1.07	1.00–1.14	0.067
Creatinine, mg/dL	9.00	3.70–21.88	<0.001	8.54	3.13–23.34	<0.001
eGFR, mL/min/1.73m^2	0.97	0.96–0.99	<0.001	1.01	0.97–1.04	0.720
Ever smoker	1.40	0.80–2.45	0.244			
Current smoker	2.14	1.19–3.86	0.011	1.90	0.91–3.96	0.085
DR	3.94	2.21–7.03	<0.001	2.11	1.04–4.26	0.038
PDR	4.38	1.55–12.37	0.005	1.48	0.39–5.59	0.561
CSME	3.50	0.38–31.84	0.267			

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TABLE 4. Risk of CKD in Patients With Presence of DR and PDR Relative to Those With No-DR

	ORs for CKD (*P* Value)			
	No-DN, $n = 731$	MA, $n = 187$	ON, $n = 53$	All, $n = 971$
No-DR	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
DR	1.35 (0.441)	2.95 (0.009)	1.80 (0.356)	2.02 (0.004)
PDR	2.13 (0.325)	4.32 (0.011)	1.80 (0.546)	4.07 (<0.001)

regression, OR 2.95 [$P = 0.009$] and OR 4.32 [$P = 0.011$], respectively) and DR and PDR are associated with CKD in the overall group of DM patients (univariate logistic regression, OR 2.02 [$P = 0.004$] and OR 4.07 [$P < 0.001$], respectively) (Table 4).

DISCUSSION

In the current study, the prevalence of DR, PDR, microalbuminuria, and overt nephropathy among type 2 DM patients were 20.0%, 3.8%, 19.3%, and 5.5%, respectively. In a nationally representative sample of US adults with diabetes aged 40 years and older, the prevalence of DR and PDR were 28.5% and 1.5%.[21] In cross-sectional analyses of the National Health and Nutrition Examination Survey from 2005 to 2008 in the United States, the prevalence of albuminuria (urine albumin/creatinine ratio higher than 30 mg/g) was 23.7%.[22] The results of the current study are largely consistent with a similar epidemiologic study performed in Spain, which showed the prevalence of DR, microalbuminuria, and overt nephropathy to be 26.11%, 17.78%, and 6.74%, respectively, in type 2 DM.[23]

The prevalence of microvascular complications varied somewhat from that found in other previous studies in Korean and Western populations. The prevalence of DR has ranged between 7.0% and 38.3% in other Korean studies.[24–27] In a previous investigation in a Korean outpatient type 2 DM cohort performed in 1995, 20% of patients had microalbuminuria and 14% had overt proteinuria.[28] In 2006, 30.3% of diabetic patients were found to have microalbuminuria in a Korean nationwide survey.[27] The prevalence of DR in Western countries has ranged between 10.6% and 36.0%.[29–34] These differences may be due to the methodology used, differences in participants' inclusion criteria, and study design (population-based studies versus clinical-setting studies).

Several risk factors appear to influence susceptibility to the microvascular complications of DM, but the roles of genetic and environmental factors are not yet completely understood. Diabetes mellitus duration, poor glycemic control, arterial hypertension, and poor lipid control have consistently been shown to correlate with DR and DN, but to date, the relationship of one diabetic microvascular complication with another has not been clearly described in the Korean population.[35–37]

A number of studies provide evidence that DR may be independently associated with the development of microalbuminuria and hence be a powerful predictor for the progression of renal damage in DM patients.[7–10] However, those have primarily been conducted in Western populations. This is the first study evaluating the relationship between DR and DN (both microalbuminuria and overt nephropathy) in a Korean population.

In the current study, an association between DR (both DR itself and PDR) and DN (both microalbuminuria and overt nephropathy) is significant in the univariate χ^2 test. In the multiple logistic regression analyses, the presence of DR shows significant association with overt nephropathy and the presence of PDR shows significant association with microalbuminuria.

Several studies have shown that the presence of DR itself may reveal patients at risk of DN. El-Asrar et al.[7] conducted a cross-sectional study that enrolled type 1 and type 2 DM patients. Multivariate logistic regression analyses indicated that patients with DR were 4.37 times more likely to have DN as those without DR. Schmechel and Heinrich[38] indicated that patients with DR exhibited proteinuria more frequently than did those without DR. Villar et al.[8] also demonstrated that DR was one of the most important risk factors for the development of incipient nephropathy in normoalbuminuric, normotensive patients with either type 1 or type 2 DM. In the EURODIAB Complications Study, DR in association with increased blood pressure was an important risk factor for the progression of DN.[9] Rossing et al.[10] demonstrated that DR may predict the development of microalbuminuria in a 10-year prospective, observational study. But these two studies enrolled patients with type 1 DM only.

Several studies have shown the prevalence of PDR, rather than DR itself, is a risk factor for DN (microalbuminuria[23,37,39] and overt nephropathy[23,39]). El-Asrar et al.[7] indicated that the prevalence of DN was found to rise with increasing severity of DR. Schmechel and Heinrich[38] also indicated that the prevalence of proteinuria increased relative to the severity of DR in type 1 and type 2 DM.

Because the results of previous studies were diverse, the results of the current study are consistent with some previous studies but not with others. This finding may be partially explained by differences in the study design and the smaller sample size compared with the previous studies. Differences in DM complications due to ethnic/racial differences between East Asian and Western populations might also explain the disparate results.

It is difficult to explain why the more severe form of DR (PDR) is not the risk factor for more severe form of DN (overt nephropathy). In our study, we defined DN by the presence of proteinuria. Proteinuria has been generally considered a hallmark of DN. However, the concept of nonproteinuric diabetic kidney disease (DKD) is emerging by several investigations published during the past decade, reporting that impaired eGFR can occur without substantial albuminuria and that DKD can manifest solely as impaired eGFR. A considerable number, between one-third and one-half, of patients with type 2 DM and impaired eGFR do not have proteinuria.[40–44] Traditionally, it was regarded that the severity of proteinuria was strongly associated with the severity of DN. With the paradigm shift, the severity of DN cannot be explained only with the severity of proteinuria.

In the current study, there was no significant association between CSME and DN. This result is inconsistent with some previous studies that have shown the prevalence rates of DN to be significantly higher among patients with DME when compared with those without DR.[7] This finding may be partially explained by the smaller sample size, especially in patients with CSME.

There also have been some previous studies that have not found an association between DR and DN.[45] It has been reported that DR and DN can occur in isolation, which suggests that there may be some fundamental differences in some patients and in some aspects of the pathogenesis. Further experimental studies, rather than epidemiological studies, would be needed to investigate the exact differences in the pathophysiology of these microvascular complications.[46]

The relationship between systolic blood pressure and DN (both microalbuminuria and overt nephropathy) is significant both in the univariate and multiple logistic regression analyses. The level of HbA1c is significantly higher in DN (both microalbuminuria and overt nephropathy). High level of HbA1c and long duration of DM are significant risk factors for overt nephropathy both in the univariate and multiple logistic regression analyses. These results are consistent with previous investigations, which have shown that, along with DM duration, HbA1c levels and blood pressure are the most important risk factors for appearance of DN.[39]

Diabetes mellitus is one of the leading causes of CKD,[1] and we hypothesized that DR could be associated with CKD. We found that DR and PDR were associated with CKD in the microalbuminuria group, and DR and PDR were risk factors for CKD in the overall group of all DM patients. However, we investigated this association only with univariate logistic regression. The results suggest that DR could be associated not only with DN but also with CKD. Few studies have demonstrated that CKD is associated with DR and it is not clear if CKD in the absence of albuminuria is associated with DR.[47–49] Sabanayagam et al.[47] demonstrated that CKD is associated with DR only in the presence of albuminuria, suggesting that CKD is more likely related to diabetes in the presence of albuminuria. Lee et al.[48] demonstrated that ischemic DR characterized with extensive capillary nonperfusion is a possible prognostic factor for the progression of CKD. Additional studies are needed to explore the relationship between DR and CKD further.

Our study has several limitations. First, the relationship between the two major microvascular complications in DM patients may vary depending on the DM treatment regimen, especially in type 2 DM patients.[37,38] We did not investigate the influence of treatment modalities, such as insulin. Second, although we excluded the participants who were younger than 30 years when diagnosed with DM and were receiving insulin therapy in the current study, it is possible that the sample does not uniformly consist of type 2 DM patients. Third, some factors, including dyslipidemia and hypertension, are not only risk factors for DN but also consequences of renal damage. Therefore, causality between these factors is impossible to infer. Fourth, the sample size here is smaller compared with some previous studies that have been carried out on this subject. In particular, the number of patients with PDR was only 37.

Despite these limitations, the current study used representative nationwide, population-based data, which enabled us to investigate the relationship between DR and DN in the Korean DM population for the first time. We found that PDR is associated with microalbuminuria and DR itself is associated with overt nephropathy. Presence of DR or PDR could be an indicator for the presence of DN in Korean patients. When an ophthalmologist finds the presence of DR or PDR, communication with an internist and/or referral to a nephrologist should be considered.

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