The Degree of Diabetic Retinopathy in Patients with Type 2 Diabetes Correlates with the Presence and Severity of Coronary Heart Disease

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Both diabetic retinopathy (DR) and coronary heart disease (CHD) are clinically significant in diabetic patients. We investigated the correlation between the severity of DR and the presence and severity of CHD among type 2 diabetic patients. A total of 175 patients who were examined at the DR clinic and underwent dual-source computed tomography (DSCT) angiography within 6 months were included. The degree of DR was graded as no DR, nonproliferative DR (NPDR), and proliferative DR (PDR). The severity of CHD and the numbers of significant stenotic coronary artery on DSCT angiography according to DR grade were assessed. The mean Agatston Calcium Score (ACS) in patients with PDR was significantly higher than other groups ($P < 0.001$). The overall odds of an ACS increase were about 4.7-fold higher in PDR group than in no DR group ($P < 0.001$). In PDR group, in comparison with in no DR, the odds of having 1 or 2 arterial involvement were 3-fold higher ($P = 0.044$), and those of having 3 were 17-fold higher ($P = 0.011$). The c-index, one of the predictability values in regression analysis model, was not significantly increased when PDR was added to classical CHD risk factors (0.671 to 0.706, $P = 0.111$). Conclusively, patients with PDR develop a greater likelihood of not only having CHD, but being more severe nature. PDR has no additional effect to classical CHD risk factors for predicting CHD.

Keywords: Coronary Heart Disease; Diabetic Retinopathy; Type 2 Diabetes

INTRODUCTION

Coronary heart disease (CHD) is a leading cause of death in patients with diabetes mellitus (1,2), and is one of the well-known macrovascular complications of diabetes. Diabetic retinopathy (DR) is also a well-known microvascular complication of diabetes and a major cause of blindness in diabetes mellitus. Hence, both CHD and DR are clinically very significant with respect to the quality of life of patients with diabetes.

There have been concerns expressed by clinicians regarding the relationships between CHD and DR, and some studies have suggested that microvascular disease may play a prominent role in CHD development in diabetes (3-6). The findings of recent studies also suggest that retinopathy is an early sign of other vascular complications and is strongly associated with the development of CHD (3,6-8). A previous study has reported that the patients with diabetes appear to have a higher prevalence of silent myocardial ischemia and asymptomatic CHD (9,10).

In this regard, an interesting question that arises from a clinical prospective is whether screening for CHD should be introduced for asymptomatic patients with DR. Until now, however, no consensus or guidelines have been established. Our present study aimed to quantitatively investigate the relationship between DR and CHD using dual-source computed tomography (DSCT), a method which has gained in popularity in recent years.

MATERIALS AND METHODS

Among the patients with type 2 diabetes who visited the DR clinic of our hospital between January 2009 and July 2011, 194 patients who underwent DSCT within 6 months of these visits were selected for retrospective analysis. After excluding 19 patients due to either a previous CHD event, defined as an incidence of myocardial infarction, a myocardial revascularization procedure (e.g., percutaneous coronary intervention or coronary artery bypass graft surgery), or incomplete medical records, 175 patients were included in the final study cohort. Information on the duration of diabetes, any history of smoking, and

any history of cardiac symptoms were obtained from the patients' medical records. Typical cardiac symptoms were defined as chest pain, dyspnea, fatigue, or diaphoresis on exertion which was relieved by rest. Systemic variables including glycated hemoglobin (HbA1c), systolic blood pressure (SBP), body mass index (BMI), lipid profile, proteinuria and glomerular filtration ratio (GFR) were also evaluated. This study was approved by the Institutional Review Board and Ethics Committee of our hospital and conformed to the tenets of the Declaration of Helsinki.

Assessment of DR grading

Fundus photography was performed using a standardized protocol for both eyes of each patient using a 45 degree non-mydriatic camera. Two photographic fields, centered on the optic disc and macula, were thereby obtained (11) and these retinal photographs were graded by two researchers in a blind manner. Disagreements between the researchers were evaluated by third assessor. DR grading was performed in accordance with the Early Treatment for Diabetic Retinopathy Study (ETDRS) severity scale and patients were thereby assigned into one of three possible groups: no DR, nonproliferative diabetic retinopathy (NPDR), or proliferative diabetic retinopathy (PDR).

Dual-source computed tomography (DSCT) and Agatston calcium score (ACS)

Coronary CT scans were performed using a dual-source CT scanner (SOMATOM Definition and Somatom Definition Flash; Siemens, Erlangen, Germany). Patients with no contraindications for β-adrenergic blocking agents and with initial heart rates greater than 65 beats per minute received an oral dose of 2.5 mg bisoprolol (Concor, Merck, Darmstadt, Germany) 1 hour before the CT examination. Two puffs (2.5 mg) of isosorbide dinitrate (Isoket Spray, UCB pharma, Monheim, Germany) were sprayed into the oral cavity before each CT examination.

Non-contrast CT scanning for calcium scoring was performed from 1 cm below the tracheal bifurcation to the diaphragm in a cranio-caudal direction. DSCT was performed in a prospective electrocardiogram (ECG)-triggering mode or retrospective ECG-gating mode with ECG-based tube current modulation. During CT acquisition, 60-80 mL of iodinated contrast (Iomeron 400; Bracco S.P.A., Italy) was injected at 4 mL/second, followed by a 40-mL saline flush. A region of interest was identified in the ascending aorta and image acquisition was automatically initiated once a selected threshold (100 HU) had been reached using bolus tracking. A standard scanning protocol was then applied and tube voltage and tube current-time product were adjusted by body size as follows: 100 kVp or 120 kVp tube voltage, 240 to 400 mAs per rotation.

The severity of CHD was determined by the degree of calcification and the numbers of significant stenotic coronary arter-

ies. The Agatston calcium score (ACS) was used to quantify the degree of coronary artery calcification. 'Significant' stenosis was defined as a greater than 50% diameter on DSCT. The left main coronary artery (LM), the left anterior descending coronary artery (LAD), the left circumflex coronary artery (LCA), and the right coronary artery (RCA) were assessed in these experiments.

Statistical analysis

Patients were divided into three groups according to the severity of DR. The mean and standard deviations were calculated for continuous variables, and comparisons between the groups were conducted using the Kruskal-Wallis test for non-continuous variables. The percentage of patients was reported for categorical variables and group comparisons were done in these instances using χ^2 test.

Multiple linear regression analyses were used to analyze the correlation between ACS and DR severity, adjusting for other attributing factors. The ACS does not follow a normal distribution, so we analyzed these scores following log transformation. Variables that showed statistically significant differences (at $P < 0.05$) by univariate analysis were then analyzed using multivariate regression analyses. The duration of diabetes and the classical CHD risk factors such as age, sex, high LDL, low HDL, total cholesterol, high systolic blood pressure, smoking were considered in univariate analysis. In addition, a proportional odds model was used to analyze the risk factors affecting the increased ACS value by categorizing these results into five groups (ACS ≥ 400, 100 ≤ ACS < 400, 10 ≤ ACS < 100, 1 ≤ ACS < 10, or 0 ≤ ACS < 1).

To analyze the correlation between the severity of DR and the number of significant stenotic vessels, we categorized our patient subjects into three groups (no artery involved, 1 or 2 arteries involved, and 3 arteries involved). Multinomial logistic regression analyses were done to analyze the risk factors affecting the numbers of significant stenotic coronary arteries. The duration of diabetes and the classical CHD risk factors were also considered in univariate analysis.

We also analyzed the correlation between the ACS and the number of significant stenotic vessels using Spearman correlation analysis. We also calculated c-index, the predictability value in multinomial logistic regression analysis, to know whether the DR could be an additional risk factor for predicting CHD. We considered classical CHD risk factors such as age, sex, BMI, total cholesterol, low HDL, SBP, smoking, with or without DR.

P value < 0.05 was considered statistically significant. Statistical analyses were performed using Statistical Analysis System (SAS) version 9.2 (SAS Inc., Cary, NC, USA).

Ethics statement

The study protocol was reviewed and approved by the institu-

tional review board of the Asan Medical Center, Seoul, Korea (IRB No. 2014-0815). Informed consent was waived by the board.

RESULTS

Baseline characteristics

Among the 175 patients we selected for analysis, 38 patients had no DR, and 88 NPDR, and 49 showed PDR. The baseline characteristics of each group are summarized in Table 1.

Among these three DR grading groups, there were significant differences in the duration of diabetes ($P < 0.001$) as well as their mean HbA1c level ($P = 0.003$). No age or gender differences were observed among groups. In addition, there were no differences in the mean systolic blood pressure (SBP) or the percentage of patients taking anti-hypertensive medication among groups. In addition, the body mass index (BMI), total cholesterol, low- density lipoprotein (LDL), high-density lipoprotein (HDL), statin intake, smoking history, and aspirin intake were not significantly different among the three groups. However, nephropathy parameters - the presence of proteinuria and the glomerular filtration ratio (GFR) - were found to be significantly related to the severity of DR ($P = 0.001$, and $P < 0.001$, respectively).

Interestingly, there were no significant differences in the experiencing of cardiac symptoms among the DR groups, when the patients were divided into three symptom categories; typical cardiac symptoms, nonspecific symptoms, and no symptoms. Forty-one patients (23%) complained of typical chest pain.

The representative case from each group is presented in Fig. 1. Fig. 1A shows the patient with no DR and no sign of coronary artery stenosis, and the total ACS was zero in this patient. Fig. 1B shows the patient with NPDR and significant stenosis in the mLAD artery (yellow arrow) and dLCX artery (green arrow). Calcified plaques are evident in the LAD artery (red arrow) and the total ACS of this case as 159.2. Fig. 1C shows the patient with PDR showing significant stenosis in the dRCA (yellow arrow), LAD artery (red arrow) and pLCX artery (green arrow) with heavy calcified plaques. The total ACS in this patient was 374.6.

We also analyzed the relationship between cardiovascular state and cardiac symptoms, and between the ACS values and the number of significant stenotic coronary arteries. The number of significant stenotic coronary arteries showed a significant relationship to the symptom severity ($P = 0.019$), but the association between the ACS and severity of symptoms was not found to be significant ($P = 0.309$). The number of significant stenotic coronary arteries and the ACS had a significantly positive correlation in a Spearman correlation analysis ($P < 0.001$), with a correlation coefficient (r) of 0.586 (Table 2 and Fig. 2).

Relationship between the DR grading and DSCT findings

When the DSCT findings for our patient subjects were analyzed and compared according to the severity of DR, we found a significant increase in the ACS ($P < 0.001$), as well as in the number of significant stenotic vessels ($P = 0.011$), as the DR severity increased (Table 3).

Table 1. Baseline characteristics of the study patients

Parameters	No DR (n = 38) (mean ± SD)	NPDR (n = 88) (mean ± SD)	PDR (n = 49) (mean ± SD)	P value
Age, yr	63.4 ± 7.3	63.8 ± 8.4	61.9 ± 11.5	0.517
Sex (M:F)	17 (45%):21 (55%)	46 (52%):42 (58%)	29 (59%):20 (41%)	0.407
HbA1c (NGSP) (%)	7.2 ± 0.9	7.8 ± 1.5	8.3 ± 1.6	0.003
HbA1c (IFCC), mmol/mol	55.0 ± 10.0	62.0 ± 17.0	67.0 ± 16.5	
LDL, mg/dL	98.5 ± 30.6	91.4 ± 34.1	91.9 ± 34.6	0.550
HDL, mg/dL	50.2 ± 9.2	51.1 ± 21.5	51.5 ± 23.5	0.956
Total cholesterol, mg/dL	182.5 ± 39.8	159.6 ± 37.1	162.2 ± 41.5	0.011
ACR, mg/g	12.1 ± 13.5	217.8 ± 779.1	1,067.2 ± 1,818.7	0.082
SBP, mmHg	127.5 ± 13.5	132.0 ± 17.1	132.4 ± 18.7	0.338
BMI, kg/m²	25.4 ± 2.8	24.5 ± 3.6	25.2 ± 3.2	0.322
DM duration, yr	8.6 ± 5.9	16.0 ± 6.8	20.3 ± 6.4	< 0.001
GFR, mL/min/1.73 m²	75.7 ± 12.5	69.8 ± 13.1	59.1 ± 23.5	< 0.001
Statin intake (N:Y)	25:15	60:28	29:20	0.476
Smoking (N:Y)	17:15	55:24	33:15	0.224
HTN on medication (N:Y)	16:22	44:44	17:32	0.216
Proteinuria (N:Y)	25:4	43:21	11:21	0.001
Renal dysfunction* (N:Y)	38:0	86:2	39:10	< 0.001
Aspirin intake (N:Y)	17:19	38:50	20:29	0.840
Cardiac symptom (Asymptomatic:Atypical:Typical)	24:8:6	53:14:20	27:7:15	0.572

The ACS, HbA1c, DM duration, and GFR and all other continuous variables were analyzed using the Kruskal Wallis test.
HbA1c, glycated hemoglobin; NGSP, national glycohemoglobin standardization program; IFCC, international federation of clinical chemistry; ACS, Agatston calcium score; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACR, albumin/creatinine ratio; SBP, systolic blood pressure; BMI, body mass index; GFR, glomerular filtration ratio; HTN, hypertension.
*Renal dysfunction was analyzed using the Fisher's exact test. All other categorical variables were analyzed by a χ^2 test.

Age, sex, and aspirin intake were found by univariate analysis to be influencing factors for the ACS. We further found that as the patient age increased by one year, the odds increased by 1.053-fold ($P = 0.001$). In male patients, these odds were significantly higher (about 2.5-fold) compared with female cases ($P = 0.001$). In patients with aspirin intake, these odds were also significantly higher (2.134-fold) compared with patients with no aspirin intake ($P = 0.007$).

When multiple linear regression analysis was conducted in a comparison with no DR cases, the log-transformed ACS was significantly high (up to 1.952) in PDR patients ($P < 0.001$), but not in NPDR cases ($P = 0.125$). We also analyzed the possible risk factors for an increased ACS using a proportional odds model. We categorized the patients into five ACS groups based on their scores (ACS ≥ 400, 100 ≤ ACS < 400, 10 ≤ ACS < 100, 1 ≤ ACS < 10, or 0 ≤ ACS < 1), and we calculated the overall odds ratio when the ACS increased from the lower level group to higher level group.

The odds of a coronary arterial involvement in the PDR group were significantly higher (about 4.7-fold) than the no DR group
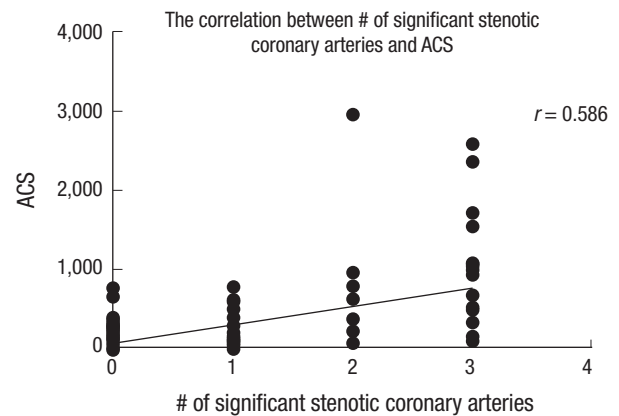

Fig. 2. Correlation between the number of significant stenotic coronary arteries and the ACS.
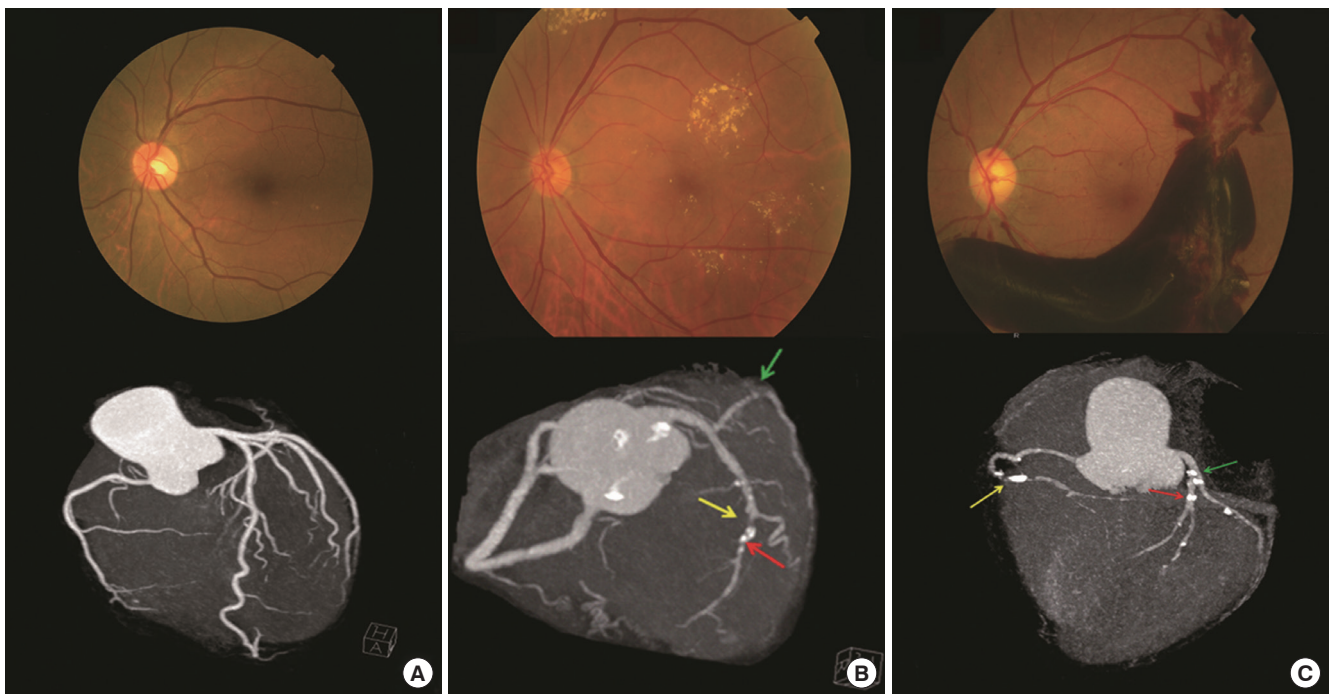ACS, Agatston calcium score.

Fig. 1. Fundus photographs and coronary CT images of representative cases in each diabetic retinopathy category. (A) A patient with no DR (top) and no sign of coronary artery stenosis. The total ACS was zero in this case. (B) A patient with NPDR (top) and significant stenosis in the mLAD artery (yellow arrow) and dLCX artery (green arrow). Calcified plaques are evident in the LAD artery (red arrow) and the total ACS of this case was 159.2. (C) A patient with PDR (top) showing significant stenosis in the dRCA (yellow arrow), LAD artery (red arrow) and pLCX artery (green arrow) with heavy calcified plaques. The total ACS in this patient was 374.6.
DR, diabetic retinopathy; NPDR, non-proliferative DR; PDR, proliferative DR; ACS, Agatston calcium score; mLAD, mid left anterior descending; dLCX, distal left circumflex; dRCA, distal right coronary artery.

Table 2. Relationship between the cardiovascular state and cardiac symptoms

Cardiovascular state	Asymptomatic	Atypical	Typical	P value
ACS (mean ± SE)	88.0 ± 322.2	74.8 ± 245.2	93.0 ± 279.2	0.309
No. of significant stenotic coronary arteries (0:1:2:3)	65:16:14:9	23:4:1:1	21:6:3:11	0.019

The ACS was analyzed using the Kruskal-Wallis test, and the number of significant stenotic coronary arteries was analyzed with the Pearson χ^2 test.
ACS, Agatston calcium score; SE, standard error.

Table 3. Relationship between the cardiovascular state and DR severity

Cardiovascular state	No DR (n = 38)	NPDR (n = 88)	PDR (n = 49)	P value
ACS (mean ± SE)	170.0 ± 510.6	177.7 ± 311.1	364.9 ± 520.3	< 0.001
No. of significant stenotic coronary arteries (0:1:2:3)	30:4:3:1	58:14:8:8	21:9:7:12	0.011

DR, diabetic retinopathy; NPDR, non-proliferative DR; PDR, proliferative DR; ACS, Agatston calcium score; SE, standard error.
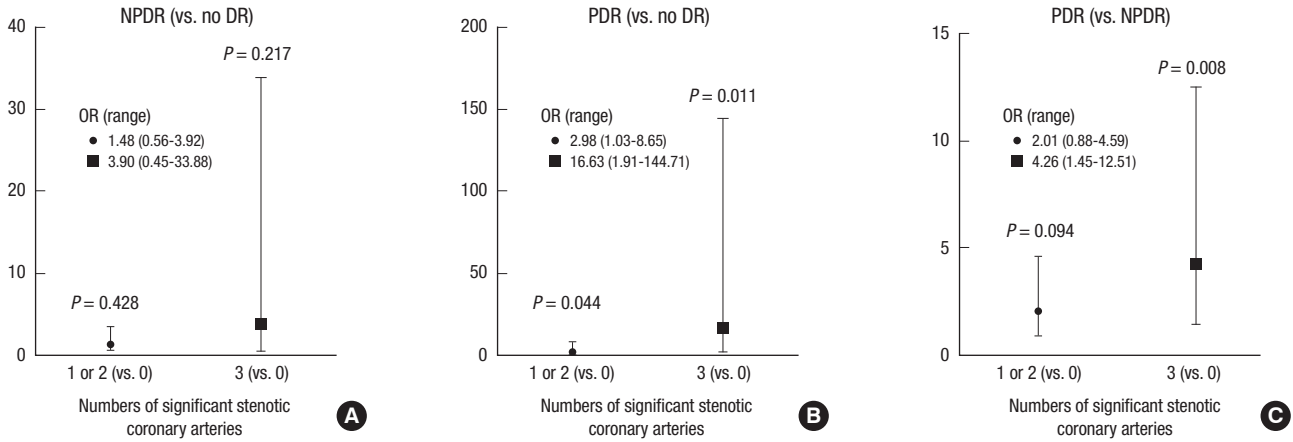

Fig. 4. Odds ratios for significantly stenotic coronary artery numbers among different DR states. DR, diabetic retinopathy.

Table 4. Proportional odds model for risk factors affecting the increase in the ACS

Parameters	OR	95% Confidence limits		P value
Age, yr	1.053	1.021	1.087	0.001
Male	2.518	1.447	4.379	0.001
NPDR (vs. no DR)	1.617	0.807	3.242	0.275
PDR (vs. no DR)	4.747	2.139	10.534	< 0.001
Aspirin intake	2.134	1.233	3.692	0.007

ACS, Agatston calcium score; OR, odds ratio; DR, diabetic retinopathy; NPDR, non-proliferative DR; PDR, proliferative DR.

Fig. 3. The proportional odds ratio for increasing ACS between PDR, NPDR and no DR group, respectively.
ACS, Agatston calcium score; DR, diabetic retinopathy; NPDR, non-proliferative DR; PDR, proliferative DR.

($P < 0.001$), whilst the odds in the NPDR group were not significantly different from those in the no DR group ($P = 0.275$; Table 4 and Fig. 3).

To analyze whether a correlation existed between the severity of DR and the number of significant stenotic vessels, we categorized the patients into three groups (no artery involved, 1 or 2 arteries involved, or 3 arteries involved). Sex and aspirin intake were found to be influencing factors for the number of coronary arteries involved, as assessed by univariate analysis. Male patients had increased odds of having three arteries involved compared with female patients (3.69-fold; $P = 0.024$) and patients who were taking aspirin had increased odds of having three arteries involved compared with those not taking aspirin (4.53-fold; $P = 0.015$).

Using multinomial logistic regression analysis, the odds of patients with PDR having three artery involvement were 16.63-fold higher ($P = 0.011$), and those of having 1 or 2 arteries involved were 2.98 times higher ($P = 0.044$), than no DR patients. When a comparison was made with NPDR patients however, the odds
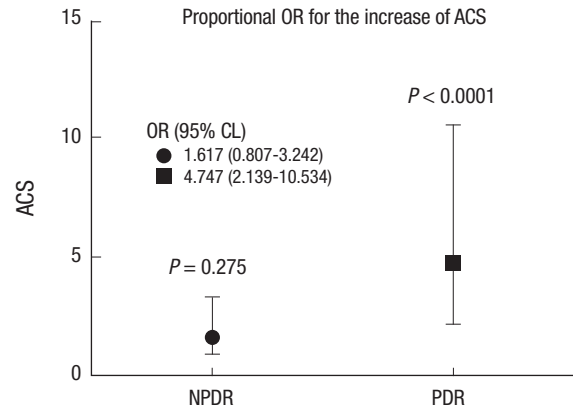
of having three arteries involved were still significantly higher (4.26-fold higher; $P = 0.008$), but of having 1 or 2 arteries involved was no longer significant ($P = 0.094$). In contrast, our NPDR patients did not show a significant increase in the odds of having a coronary artery involvement over the no DR patients (Table 5 and Fig. 4).

When we categorized ACS into five groups (ACS ≥ 400, 100 ≤ ACS < 400, 10 ≤ ACS < 100, 1 ≤ ACS < 10, or 0 ≤ ACS < 1) and did multinomial logistic regression analysis, the c-index was not significantly increased from 0.671 (without PDR) to 0.706 (with PDR, $P = 0.111$) (Table 6).

Table 5. Multinomial logistic regression analysis of significantly stenotic coronary artery numbers

Parameters	No. of coronary arteries involved	OR	OR_LL	OR_UL	P value
Male (vs. female)	1 or 2 (vs. 0)	1.56	0.76	3.19	0.224
	3 (vs. 0)	3.69	1.19	11.47	0.024
NPDR (vs. no DR)	1 or 2 (vs. 0)	1.48	0.56	3.91	0.428
	3 (vs. 0)	3.90	0.45	33.88	0.217
PDR (vs. NPDR)	1 or 2 (vs. 0)	2.01	0.88	4.59	0.094
	3 (vs. 0)	4.26	1.45	12.51	0.008
PDR (vs. no DR)	1 or 2 (vs. 0)	2.98	1.03	8.65	0.044
	3 (vs. 0)	16.63	1.91	144.71	0.011
Aspirin intake (vs. no intake)	1 or 2 (vs. 0)	1.49	0.72	3.07	0.279
	3 (vs. 0)	4.53	1.35	15.26	0.015

OR, odds ratio; LL, lower limit; UL, upper limit; DR, diabetic retinopathy; NPDR, non-proliferative DR; PDR, proliferative DR.

Table 6. The c-index in multinomial logistic regression analysis for predicting CHD*

Parameters	Regression model with DR (c-index: 0.706)			Regression model without DR (c-index: 0.671)		
	Estimate	95% CL	P value	Estimate	95% CL	P value
Age	0.948	0.917-0.981	0.002	0.954	0.923-0.985	0.004
Male (vs. female)	0.311	0.153-0.633	0.001	0.28	0.139-0.563	< 0.001
BMI	1.021	0.935-1.116	0.642	1.01	0.925-1.102	0.828
Total cholesterol	0.998	0.99-1.006	0.642	1	0.992-1.007	0.965
HDL	1.007	0.992-1.021	0.376	1.007	0.992-1.021	0.371
SBP	0.993	0.976-1.011	0.453	0.994	0.977-1.011	0.479
Smoking	1.355	0.643-2.857	0.437	1.573	0.761-3.251	0.395
NPDR (vs. no DR)	0.697	0.325-1.494	0.165			
PDR (vs. no DR)	0.215	0.09-0.515	< 0.001			

ACS was categorized into five groups (ACS ≥ 400, 100 ≤ ACS < 400, 10 ≤ ACS < 100, 1 ≤ ACS < 10, or 0 ≤ ACS < 1).
CHD, coronary heart disease; ACS, Agatston calcium score; DR, diabetic retinopathy; CL, confidence limits; BMI, body mass index; HDL, high-density lipoprotein; SBP, systolic blood pressure; NPDR, non-proliferative DR; PDR, proliferative DR.
*c-index increase: 0.035, P value = 0.111.

DISCUSSION

It has been speculated that the pathologic processes that occur at the microvascular level may contribute to the pathogenesis of macrovascular complications such as CHD. One hypothesis in this regard is that retinal microvascular abnormalities may reflect an early subclinical coronary or cerebral microvasculature and predispose the development of clinical cardiovascular events (3). There have been findings in several studies supporting the proposition that DR is significantly associated with CHD or increased cardiovascular events (3-6,9,12,13). A prospective cohort study by Cheung et al. (3) has reported that the presence of DR is associated with a 2-fold higher risk of CHD and 3-fold higher risk of fatal CHD and that this is independent of the glycemic level or other cardiovascular risk factors. Rosenson et al. (4) have shown that microvascular diseases such as nephropathy, retinopathy and neuropathy can predict macrovascular episodes such as cardiovascular events in patients with type 2 diabetes.

Rong et al. (13) have reported from coronary 64-slice multidetector computed tomography angiography analysis of Chinese patients with type 2 diabetes that DR is associated with coronary atherosclerosis (CAS). The incidence and progression of DR were also associated with the severity and extent of CAS. These authors further reported that CAS is significantly associated with the presence of DR and that its prevalence, determined by the number of CAS vessels, showed significant differences among NPDR, pre-PDR and PDR patients.

Our current results are supportive of DR as a risk factor for CHD and that the severity of DR is strongly associated with an increased CHD risk. The major difference between the findings of our present study and those of previous studies is that we evaluated the ACS and the number of stenotic coronary arteries as a CHD status using DSCT. This method allows the visualization of coronary arteries at raised heart rates and thus reduces the number of inaccessible coronary artery segments because of motion effects when using coronary 64-slice multidetector computed tomography angiograph (14,15). In addition, DSCT enables the coronary calcium score to be determined as is the case in other coronary CT angiography methods. The coronary calcium score is known as a strong predictor of incident CHD and affords more accurate predictive information beyond that provided by standard risk factors (15).

Our current study findings show that the log ACS values were significantly higher (2-fold) in PDR patients compared with no DR patients (P < 0.001). Additionally, we categorized the ACS

values of our patients into five groups (ACS ≥ 400, 100 ≤ ACS < 400, 10 ≤ ACS < 100, 1 ≤ ACS < 10, or 0 ≤ ACS < 1) in accordance with a previous study (15). We then used a proportional odds model to calculate the overall odds ratio when the ACS increased from the lower to higher level grouping. The odds of a coronary arterial involvement were significantly higher (4.7-fold) in the PDR group compared with the no DR group ($P < 0.001$), whereas these odds in the NPDR group did not differ significantly from those of the no DR group ($P = 0.275$). Based on these findings, PDR patients have not just a higher ACS but also a higher likelihood of being in a higher ACS group than patients without DR. In addition, the odds of having a 1 or 2 coronary artery involvement in the PDR group were found to be 3-fold greater than the no DR group ($P = 0.044$). Additionally, the odds of having a 3 coronary artery involvement were 17-fold higher in the PDR patients compared with the no DR cases ($P = 0.011$). In contrast, our NPDR patients did not show a significant increase in their odds having a 1, 2 or 3 coronary arterial involvement over the no DR group. Accordingly, our study findings indicate that patients with PDR have a higher probability of not only having CHD, but also developing more severe CHD compared with patients without DR.

We also investigated and compared the c-index, one of the predictability values in regression analysis model, between models with classical CHD risk factors only and with PDR added as an additional risk factor, because we want to know whether PDR could have any additional effect to classical CHD risk factors for predicting CHD. In regression model with classical CHD risk factors and PDR, PDR was also a significant and independent risk factor ($P < 0.001$) for predicting CHD, like results above already seen. But the c-index was not significantly increased ($P = 0.111$) when PDR was added to classical CHD risk factors. Our results indicate that PDR can be another independent risk factor for predicting CHD compared with no DR, but PDR has no additional effect to increase the predictability of classical CHD risk factors.

With regard to aspirin intake, our current results indicated the patients in our study cohort who were taking this drug showed a higher risk of CHD than patients who were not. In general, many previous studies have reported that aspirin intake has a preventive effect in the case of CHD (16,17). We speculate that patients in our cohort with a higher risk of CHD might have been taking aspirin more often, which may have skewed our findings.

Silent ischemia is a serious medical problem that can potentially lead to death. The fact that patients with CHD in diabetes mellitus are commonly asymptomatic has been well documented in previous studies (9,10). In current study, 39 of our 104 asymptomatic patients (37.5%) had CHD, and 9 patients (8.7%) had three vessels disease. In addition, the ACS values in our asymptomatic patients were not found to be significantly different from those in the atypical or typical symptomatic patients. Hence, the significance of CHD in asymptomatic patients is as

important as it is in symptomatic patients. At baseline, 104 of our patients (59.8%) were asymptomatic for CHD and no differences in the symptom ratios were found among groups. Thus, we speculate that the DR status is important evidence to consider if recommending a screen for CHD, regardless of the presenting symptoms. In clinical situations, we contend that more attention needs to be paid in this regard to asymptomatic patients with diabetes, particularly when they have PDR.

There have been some guidelines produced by the American Diabetes Association (ADA), the ALFEDIAM-SFC (French-speaking Societies for diabetes & cardiology) and CRI (Cardiac Radionuclide Imaging) for the screening of silent myocardial ischemia in asymptomatic patients with a normal resting electrocardiogram in type 2 diabetes (1,18,19). In addition, Cosson et al. (20) have shown that the diagnostic value of these guidelines is improved by taking account of a male gender and the retinopathy status. However, the guidelines for the evaluation of CHD risk in diabetes have not been clearly defined yet. Since all patients with diabetes are recommended to have regular check-ups with ophthalmologists, we believed it would be beneficial for the patients if the ophthalmologists could identify any predictors for CHD. In this regard, we speculate that the central finding of our current study of the correlation between DR grade and the severity of CHD could be a useful guideline in the future.

Our present report is a single-centered, retrospective, and cross-sectional study and has some limitations of note. The fundus photography, which we used to grade DR, is likely to have many errors, although it could be obtained and interpreted by following standardized protocols. Coronary CT angiography has become more popular to date, but only small proportion of patients with diabetes currently undergo this procedure, and it is especially rare for asymptomatic patients to do so. In addition, not all patients with diabetes are given an ophthalmologic exam. Therefore, our patient number was small and a multi-centered prospective study with a larger cohort is needed in the future.

In summary, we find here that patients with type 2 diabetes and PDR have more severe coronary arterial calcification, and a greater likelihood of not only having CHD but being more severe nature than patients without DR. PDR has no additional effect to classical CHD risk factors for predicting CHD. We conclude that PDR can be a predictor for CHD in asymptomatic patients with type 2 diabetes, and a screen for CHD in PDR patients is reasonable and advisable.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Concept and design: Um T, Lee DH, Yoon YH. Acquisition of

data: Um T. Analysis and interpretation of data: Um T, Lee DH, Kang JW, Kim EY, Yoon YH. Drafting manuscripts: Um T, Lee DH. Final approval: all authors.

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