Original Article
Cardiovascular Risk/Epidemiology

Diabetes Metab J 2020;44:470-479
https://doi.org/10.4093/dmj.2019.0073
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

Impact of Diabetes Control on Subclinical Atherosclerosis: Analysis from Coronary Computed Tomographic Angiography Registry

Gyung-Min Park[1], Chang Hoon Lee[2], Seung-Whan Lee[3], Sung-Cheol Yun[4], Young-Hak Kim[3], Yong-Giun Kim[1], Ki-Bum Won[1], Soe Hee Ann[1], Shin-Jae Kim[1], Dong Hyun Yang[5], Joon-Won Kang[5], Tae-Hwan Lim[5], Eun Hee Koh[6], Woo Je Lee[6], Min-Seon Kim[6], Joong-Yeol Park[6], Hong-Kyu Kim[7], Jaewon Choe[7], Sang-Gon Lee[1]

[1]Department of Cardiology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan,
[2]Department of Cardiology, Veterans Health Service Medical Center, Seoul,
Departments of [3]Cardiology, [4]Biostatistics, [5]Radiology, [6]Endocrinology, [7]The Health Screening and Promotion Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: There are limited data on the impact of diabetes control on the risk of subclinical coronary atherosclerosis.
Methods: We analyzed 6,434 consecutive asymptomatic individuals without previous history of coronary artery disease who underwent coronary computed tomographic angiography (CCTA) (mean age, 53.7±7.6 years and 4,694 men [73.0%]). The degree and extent of subclinical coronary atherosclerosis were assessed by CCTA, and ≥50% diameter stenosis was defined as significant. A cardiac event was defined as a composite of all-cause death, myocardial infarction, unstable angina, or coronary revascularization. Study participants were categorized as normal (n=5,319), controlled diabetes (glycosylated hemoglobin [HbA1c] <7%, n=747), or uncontrolled diabetes (HbA1c ≥7%, n=368), respectively.
Results: Compared with normal individuals, there were no statistically significant differences in the risk of for any atherosclerotic plaque (odds ratio [OR], 1.16; 95% confidence interval [CI], 0.98 to 1.38; P=0.086) and significant coronary artery stenosis (OR, 1.08; 95% CI, 0.82 to 1.42; P=0.583) in controlled diabetic individuals. In contrast, uncontrolled diabetic individuals had consistently higher risks of any atherosclerotic plaque (OR, 2.16; 95% CI, 1.70 to 2.75; P<0.001) and significant coronary artery stenosis (OR, 3.34; 95% CI, 2.52 to 4.43; P<0.001) than normal individuals. During a follow-up of median 5.4 years, there was no significant difference in cardiac events between normal and controlled diabetic individuals (P=0.365). However, uncontrolled diabetes was associated with an increased risk of cardiac events compared with normal individuals (P<0.001) and controlled diabetic individuals (P=0.023).
Conclusion: Asymptomatic uncontrolled diabetes was associated with significant subclinical coronary atherosclerosis with subsequent high risk for cardiac events.

Keywords: Atherosclerosis; Coronary artery disease; Diabetes complications; Diabetes mellitus

INTRODUCTION

Glycemic control is fundamental to diabetes management [1]. Previous studies have demonstrated that improved glycemic control is associated with significantly reduced onset or progression of microvascular complications in diabetic individuals [2-6]. In addition, individuals with diabetes showed a higher prevalence, extent, and severity of coronary atherosclerosis than those without [7-9]. Coronary artery disease (CAD) is a leading cause of death among diabetic individuals [10]. Recent

Corresponding author: Seung-Whan Lee https://orcid.org/0000-0002-2662-5952
Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
E-mail: seungwlee@amc.seoul.kr

Received: Apr. 23, 2019; Accepted: Aug. 7, 2019

long-term follow-up studies have also shown cardiovascular benefits of intensive glycemic control [3,11]. However, there are limited data regarding the impact of the diabetes control on the risk of subclinical coronary atherosclerosis in asymptomatic individuals. With the advent of multidetector row computed tomography (CT), coronary computed tomographic angiography (CCTA) has proven to be effective in providing the comprehensive evaluation of coronary atherosclerosis, including lesion location, severity and plaque characteristics [12]. Thus, in this study, we sought to evaluate the impact of diabetes control on the risk of subclinical coronary atherosclerosis through a large cohort of asymptomatic Korean individuals who voluntarily underwent CCTA.

METHODS

Study population

In total, 9,269 consecutive South Korean individuals aged 20 years and older who had undergone self-referral CCTA evaluation as part of a general health examination in the Health Screening and Promotion Center at Asan Medical Center from January 2007 to December 2011. Among these, 7,129 individuals (76.9%) agreed to participate in this study. Possible risks associated with CCTA were explained and informed consent was obtained. Exclusion criteria include subjects with (1) a previous history of angina or myocardial infarction; (2) abnormal rest electrocardiographic results, i.e., pathological Q waves, ischemic ST segments or T wave changes, or left bundle-branch blocks; (3) insufficient medical records; (4) structural heart diseases; (5) a prior history of open heart surgery or percutaneous coronary intervention; (6) a previous cardiac procedure; or (7) renal insufficiency (creatinine >1.5 mg/dL). Finally, 6,434 subjects were enrolled (Supplementary Fig. 1). The study was approved by the local Institutional Review Board of the Asan Medical Center, Seoul, Korea (approval number: 2016-1068).

The demographic information was collected from a database maintained by the Health Screening and Promotion Center at the Asan Medical Center. Medical history including angina, myocardial infarction, stroke, structural heart disease, open heart surgery, percutaneous coronary intervention, previous cardiac procedures, diabetes mellitus, hypertension, or hyperlipidemia; a family history of CAD; and smoking status was taken from the responses in the systemized self-report questionnaire issued prior to the general health examination. A family history of CAD was defined as having a first-degree relative of any age on the self-report questionnaire [13]. Patients with diabetes was defined as (1) subjects with a self-reported history of diabetes and/or treatment with dietary modification, or use of anti-diabetic medication on the systemized questionnaire and (2) those with a fasting plasma glucose (FPG) ≥126 mg/dL or a glycosylated hemoglobin (HbA1c) level ≥6.5% [13,14]. By their diabetes control, participants with diabetes were classified as controlled diabetes (diabetes with HbA1c <7%) and uncontrolled diabetes (diabetes with HbA1c ≥7%), respectively [1]. Those without diabetes were categorized as normal group. Hypertension was defined as a blood pressure ≥140/90 mm Hg or a self-reported history of hypertension and/or use of anti-hypertensive medication. Hyperlipidemia was also defined as total cholesterol ≥240 mg/dL a self-reported history of hyperlipidemia and/or use of anti-hyperlipidemic treatment.

Clinical and laboratory measurements

Height and weight were obtained while subjects wore light clothing without shoes. The body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Obesity was defined as a BMI of ≥25.0 kg/m^2 using the cut-offs of BMI for Asian population. The waist circumference (cm) was measured midway between the costal margin and the iliac crest at the end of a normal expiration. The blood pressure was measured on the right arm after a rest of ≥5 minutes using an automatic manometer with an appropriate cuff size. Left ventricular ejection fraction was measured by echocardiography. After overnight fasting, early morning blood samples were drawn from the antecubital vein into vacuum tubes and subsequently analyzed in the central, certified laboratory of the Asan Medical Center. Measurements included the concentrations of FPG, uric acid, creatinine, high-sensitivity C-reactive protein (hs-CRP), and several lipid parameters. Fasting total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol (LDL-C), triglyceride, uric acid and creatinine were measured by an enzymatic colorimetric method using a Toshiba 200FR Neo (Toshiba Medical System Co. Ltd., Tokyo, Japan). FPG were measured by an enzymatic colorimetric method using a Toshiba 200 FR autoanalyzer (Toshiba). Ion-exchange high-performance liquid chromatography (Bio-Rad Laboratories Inc., Hercules, CA, USA) was used to measure HbA1c levels. Serum hs-CRP level was measured according to a high-sensitivity assay by using a latex particle–enhanced immunoturbidometric assay (Roche Diag-

nostics, Mannheim, Germany). All enzyme activities were measured at 37°C [15].

CCTA image acquisition and analysis

CCTA was conducted using either single-source 64-slice CT (LightSpeed VCT; GE, Milwaukee, WI, USA) or dual-source CT (Somatom Definition; Siemens, Erlangen, Germany). Subjects with no contraindication to β-adrenergic blocking agents and with an initial heart rate 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. CT scanning was performed in the prospective electrocardiogram (ECG)-triggering mode or the retrospective ECG-gating mode with ECG-based tube current modulation. Two puffs (2.5 mg) of isosorbidedinitrate (Isoket spray; Schwarz Pharma, Monheim, Germany) were sprayed into the patient's oral cavity before contrast injection. During CCTA acquisition, 60 to 80 mL of iodinated contrast (Iomeron 400; Bracco, Milan, Italy) was injected at 4 mL/second, followed by a 40 mL saline flush. A region of interest was placed 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 used, and the tube voltage and tube current-time product were adjusted according to the patient's body size as follows: 100 or 120 kVp tube voltage; 240 to 400 mAs per rotation (dual-source CT); and 400 to 800 mA (64-slice CT) tube current [12].

All CCTA scans were analyzed using a dedicated workstation (Advantage Workstation, GE; or Volume Wizard, Siemens) by experienced cardiovascular radiologists (D.H.Y., J.W.K., and T.H.L.). According to the guidelines of the Society of Cardiovascular Computed Tomography, a 16-segment coronary artery tree model was used [16]. A coronary artery calcium score was measured as described, with categorized by scores of 0, 1 to 10, 11 to 100, 101 to 400, and >400 [17]. Plaques were defined as structures >1 mm^2 within and/or adjacent to the vessel lumen, which could be clearly distinguished from the lumen and surrounding pericardial tissue. Plaques containing calcified tissue involving more than 50% of the plaque area (density >130 HU) were classified as calcified, plaques with <50% calcium were classified as mixed, and plaques without calcium were classified as non-calcified lesions [18]. The contrast-enhanced portion of the coronary lumen was semiautomatically traced at the site of maximal stenosis and compared with the mean value of the proximal and distal reference sites [19]. Stenosis ≥50% was defined as significant. The overall plaque burden was determined from coronary artery plaque scores calculated from modified Duke prognostic scores, segment stenosis scores, and segment involvement scores, as described [20]. In addition, high-risk CAD was defined as at least 2-vessel coronary disease with proximal left anterior descending (LAD) artery involvement, 3-vessel disease, or left main (LM) disease [21].

Clinical outcomes

Follow-up clinical data were obtained by a review of medical records or telephone interviews using trained personnel through to the end of June 2017. A cardiac event was defined as a composite of all-cause death, myocardial infarction, unstable angina requiring hospitalization, or coronary revascularization. The diagnosis of myocardial infarction was based on the presence of new Q waves in at least two contiguous leads, or an elevation of creatine kinase or its myocardial band isoenzyme to at least three times the upper limit of the normal range at follow-up. Revascularization was performed if there was a stenosis of at least 50% of the diameter noted on invasive coronary angiography with a positive stress test result or if there was a stenosis of at least 70% seen on invasive coronary angiography [22].

Statistical analysis

Categorical variables are expressed as frequencies with percentages, and continuous variables as the mean and standard deviation. Between-group comparisons were performed by using the Pearson's chi-square test or Fisher's exact test for categorical variables, and by using the one-way analysis of variance or Kruskal-Wallis test for numerical variables, as appropriate. Logistic regression analyses were performed to evaluate the independent relationships between the diabetes control and subclinical coronary atherosclerosis on CCTA. For the multivariable analyses, we adjusted clinically and statistically important covariates such as age, sex, obesity, hypertension, hyperlipidemia, current smoking, a family history of CAD, and hs-CRP. Unadjusted and adjusted odds ratios with 95% confidence intervals for the logistic regression were calculated. Survival curves were assessed using the Kaplan-Meier method and compared using the log-rank test. All reported *P* values are two sided, and *P* values of <0.05 were considered statistically significant. Data manipulation and statistical analyses were conducted using the SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Population characteristics

The mean age of study participants was 53.7±7.6 years and 4,694 (73.0%) were male. Of them, 5,319, 747, and 368 participants were categorized as normal, controlled diabetes, and uncontrolled diabetes, respectively. The baseline characteristics of the study population according to the diabetes control are listed in Table 1, Supplementary Table 1. In controlled diabetes, the mean FPG and HbA1c were 121.8±17.7 mg/dL and 6.2%±0.5%. On the other hand, in uncontrolled diabetes, the mean FPG and HbA1c were 158.6±40.8 mg/dL and 8.1%±1.2%.

CCTA findings

CCTA findings according to the diabetes control are shown (Table 2, Supplementary Table 2). A total of 236 coronary segments (0.2%) were not interpretable due to artifacts. There was significant difference in CACS according to the diabetes control ($P<0.001$). The prevalence of any atherosclerotic, calcified, non-calcified, or mixed plaque increased with the diabetes control (P for all<0.001). Plaque burden scores such as segment involvement score, segment stenosis score, and modified Duke prognostic score also increased with the diabetes control (P for all<0.001). Of study participants, 494 (7.7%) had significant coronary arteries stenosis (≥50% diameter stenosis) in at

Table 1. Baseline characteristics of study participants according to the diabetes control

Variable	Normal	Controlled diabetes	Uncontrolled diabetes	*P* value
No. of patients	5,319	747	368	
Demographics				
Age, yr	53.2±7.5	55.7±7.5	55.8±7.6	<0.001
Gender				
Men	3,772 (70.9)	627 (83.9)	295 (80.2)	<0.001
Women	1,547 (29.1)	120 (16.1)	73 (19.8)	
Clinical characteristics or coexisting conditions				
Body mass index, kg/m^2	24.5±2.9	25.4±2.8	25.5±3.3	<0.001
Obesity	2,226 (41.9)	405 (54.3)	194 (52.9)	<0.001
Waist circumference, cm	85.2±8.3	88.7±7.6	89.1±8.4	<0.001
Systolic blood pressure, mm Hg	119.5±12.9	122.8±13.3	124.4±14.3	<0.001
Diastolic blood pressure, mm Hg	76.6±10.5	78.1±10.1	78.3±10.1	<0.001
Hypertension	1,772 (33.3)	407 (54.5)	173 (47.0)	<0.001
Hyperlipidemia	1,508 (28.4)	333 (44.6)	162 (44.0)	<0.001
Current smoker	1,186 (22.3)	207 (27.7)	132 (35.9)	<0.001
Previous stroke	39 (0.7)	13 (1.7)	4 (1.1)	0.019
Family history of CAD[a]	846 (15.9)	94 (12.6)	43 (11.7)	0.009
Total cholesterol, mg/dL	197.3±33.0	186.1±37.8	187.6±40.3	<0.001
LDL-C, mg/dL	123.1±29.1	112.6±32.4	113.1±33.8	<0.001
HDL-C, mg/dL	54.0±13.7	51.3±12.4	48.4±11.8	<0.001
Triglyceride, mg/dL	128.9±76.9	149.1±102.5	180.0±136.6	<0.001
Creatinine, mg/dL	0.9±0.2	0.9±0.1	0.9±0.2	0.028
Uric acid, mg/dL	5.6±1.4	5.7±1.3	5.3±1.3	<0.001
hs-CRP ≥2 mg/dL, %	42 (0.8)	9 (1.2)	7 (1.9)	0.060
Ejection fraction, %	63.3±4.1	63.4±4.0	63.6±4.4	0.388

Values are presented as mean±standard deviation or number (%).
CAD, coronary artery disease; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein.
[a]CAD in a first-degree relative of any age.

Table 2. Coronary computed tomographic angiographic findings according to the diabetes control

Characteristic	Normal	Controlled diabetes	Uncontrolled diabetes	*P* value
Mean coronary artery calcium score	33.0±123.5	71.6±203.4	90.6±174.8	<0.001
Coronary artery calcium score classification				<0.001
0	3,610 (68.1)	381 (51.3)	154 (41.8)	
1–10	470 (8.9)	91 (12.2)	37 (10.1)	
11–100	794 (15.0)	149 (20.1)	85 (23.1)	
101–400	330 (6.2)	89 (12.0)	71 (19.3)	
>400	97 (1.8)	33 (4.4)	21 (5.7)	
Any atherosclerotic plaque	2,047 (38.5)	404 (54.1)	240 (65.2)	<0.001
Plaque characteristics				
Calcified plaque	1,342 (25.2)	301 (40.3)	167 (45.4)	<0.001
Non-calcified plaque	903 (17.0)	152 (20.3)	125 (34.0)	<0.001
Mixed plaque	392 (7.4)	99 (13.3)	79 (21.5)	<0.001
Segment involvement score	0.9±1.6	1.5±2.0	2.2±2.4	<0.001
Segment stenosis score	0.5±1.7	0.9±2.3	1.8±3.1	<0.001
Modified Duke prognostic score	1.2±0.6	1.2±0.7	1.5±1.0	<0.001
Significant stenosis	336 (6.3)	75 (10.0)	83 (22.6)	<0.001
One-vessel disease	251 (4.7)	54 (7.2)	63 (17.1)	<0.001
Multi-vessel disease	85 (1.6)	21 (2.8)	20 (5.4)	<0.001
Significant stenosis in the left main or proximal LAD artery	118 (2.2)	27 (3.6)	25 (6.8)	<0.001
High-risk coronary artery disease[a]	85 (1.6)	18 (2.4)	22 (6.0)	<0.001

Values are presented as mean±standard deviation or number (%).
LAD, left anterior descending.
[a]Defined as at least 2-vessel coronary disease with proximal left anterior descending artery involvement, 3-vessel disease, or left main disease.

least one coronary artery on CCTA. The prevalence of significant stenosis, multi-vessel disease, significant stenosis in the LM or proximal LAD artery, high-risk CAD significantly increased according to the diabetes control (*P* for all<0.001).

Association between the diabetes control and subclinical atherosclerosis

Controlled diabetic individuals had more calcified and mixed plaques than the normal individuals. However, there were no statistically significant differences in the adjusted odds ratios for any atherosclerotic and non-calcified plaque, significant stenosis, multi-vessel disease, significant stenosis in the LM or proximal LAD, and high-risk CAD between the normal and controlled diabetic individuals. On the other hand, uncontrolled diabetic individuals had significantly associated with any subclinical coronary atherosclerosis compared with normal individuals (*P* for all<0.05) (Table 3).

Clinical outcomes

Supplementary Fig. 2 shows the study flow. During the follow-up period (median 5.4 years [interquartile range, 4.4 to 6.4 years]), a total of 209 cardiac events occurred in 193 patients: 67 all-cause deaths, five non-fatal myocardial infarctions, 15 acute coronary syndrome requiring hospitalization, and 122 coronary revascularizations (Table 4, Supplementary Table 3). Fig. 1 shows Kaplan-Meier survival curves according to the diabetes control. The 6-year cardiac event-free survival rates were 97.2%±0.2% in normal individuals, 96.4%±0.7% in controlled diabetic individuals, and 93.9%±1.3% in uncontrolled individuals (log-rank *P*<0.001). There was no significant difference in cardiac events between normal and controlled diabetic individuals (*P*=0.365). However, uncontrolled diabetes was associated with an increased risk of cardiac events compared with normal individuals (*P*<0.001) and controlled diabetic individuals (*P*=0.023).

Table 3. Univariable and multivariable analyses of each coronary computed tomographic angiography variables, corrected for clinical risk factors

Variable	Univariable		Multivariable	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Any atherosclerotic plaque				
Uncontrolled diabetes	3.00 (2.40–3.74)	<0.001	2.16 (1.70–2.75)	<0.001
Controlled diabetes	1.88 (1.61–2.20)	<0.001	1.16 (0.98–1.38)	0.086
Normal (reference: normal)	1	-	1	-
Calcified plaque				
Uncontrolled diabetes	2.46 (1.99–3.05)	<0.001	1.77 (1.40–2.23)	<0.001
Controlled diabetes	2.00 (1.71–2.34)	<0.001	1.29 (1.08–1.53)	0.004
Normal (reference: normal)	1	-	1	-
Non-calcified plaque				
Uncontrolled diabetes	2.52 (2.00–3.16)	<0.001	2.03 (1.60–2.57)	<0.001
Controlled diabetes	1.25 (1.03–1.51)	0.023	0.90 (0.74–1.10)	0.323
Normal (reference: normal)	1	-	1	-
Mixed plaque				
Uncontrolled diabetes	3.44 (2.63–4.50)	<0.001	2.59 (1.95–3.43)	<0.001
Controlled diabetes	1.92 (1.52–2.43)	<0.001	1.32 (1.04–1.69)	0.025
Normal (reference: normal)	1	-	1	-
Significant stenosis in at least one coronary artery				
Uncontrolled diabetes	4.32 (3.30–5.65)	<0.001	3.34 (2.52–4.43)	<0.001
Controlled diabetes	1.66 (1.27–2.15)	<0.001	1.08 (0.82–1.42)	0.583
Normal (reference: normal)	1	-	1	-
Multi-vessel disease				
Uncontrolled diabetes	3.54 (2.15–5.83)	<0.001	2.51 (1.50–4.22)	0.001
Controlled diabetes	1.78 (1.10–2.89)	0.019	1.05 (0.63–1.75)	0.844
Normal (reference: normal)	1	-	1	-
Significant stenosis in the left main or proximal left anterior descending artery				
Uncontrolled diabetes	3.21 (2.06–5.01)	<0.001	2.39 (1.51–3.79)	<0.001
Controlled diabetes	1.65 (1.08–2.53)	0.021	1.06 (0.68–1.66)	0.786
Normal (reference: normal)	1	-	1	-
High-risk coronary artery disease[a]				
Uncontrolled diabetes	3.92 (2.42–6.34)	<0.001	2.76 (1.68–4.56)	<0.001
Controlled diabetes	1.52 (0.91–2.54)	0.110	0.90 (0.52–1.54)	0.692
Normal (reference: normal)	1	-	1	-

Covariates in the multivariable model include age, sex, obesity, hypertension, hyperlipidemia, current smoking, family history of coronary artery disease, and high-sensitivity C-reactive protein ≥2 mg/L.
CI, confidence interval.
[a]Defined as at least 2-vessel coronary disease with proximal left anterior descending artery involvement, 3-vessel disease, or left main disease.

DISCUSSION

The main findings of this study were as follows: (1) in asymptomatic individuals, uncontrolled diabetes was independently associated with significant subclinical coronary atherosclerosis compared with normal and controlled diabetic individuals; (2)

Table 4. Clinical outcomes according to the diabetes control

Variable	Normal (*n*=5,319)	Controlled diabetes (*n*=747)	Uncontrolled diabetes (*n*=368)	*P* value[a]
Cardiac event				
Death/myocardial infarction/unstable angina/ coronary revascularization	145 (2.7)	25 (3.3)	23 (6.3)	<0.001
Clinical event				
Death	52 (1.0)	9 (1.2)	6 (1.6)	0.464
Myocardial infarction	3 (0.1)	2 (0.3)	0 (0)	0.133
Unstable angina	11 (0.2)	2 (0.3)	2 (0.5)	0.414
Coronary revascularization	90 (1.7)	15 (2.0)	17 (4.6)	<0.001
Early revascularization (≤90 days)	50 (0.9)	11 (1.5)	12 (3.3)	<0.001
Late revascularization (>90 days)	40 (0.8)	4 (0.5)	5 (1.4)	0.302
Death/myocardial infarction/unstable angina	65 (1.2)	13 (1.7)	8 (2.2)	0.197
Death/myocardial infarction/unstable angina/late revascularization	97 (1.8)	14 (1.9)	11 (3.0)	0.292

Values are presented as number (%).
[a]*P* values were calculated using the log-rank test.

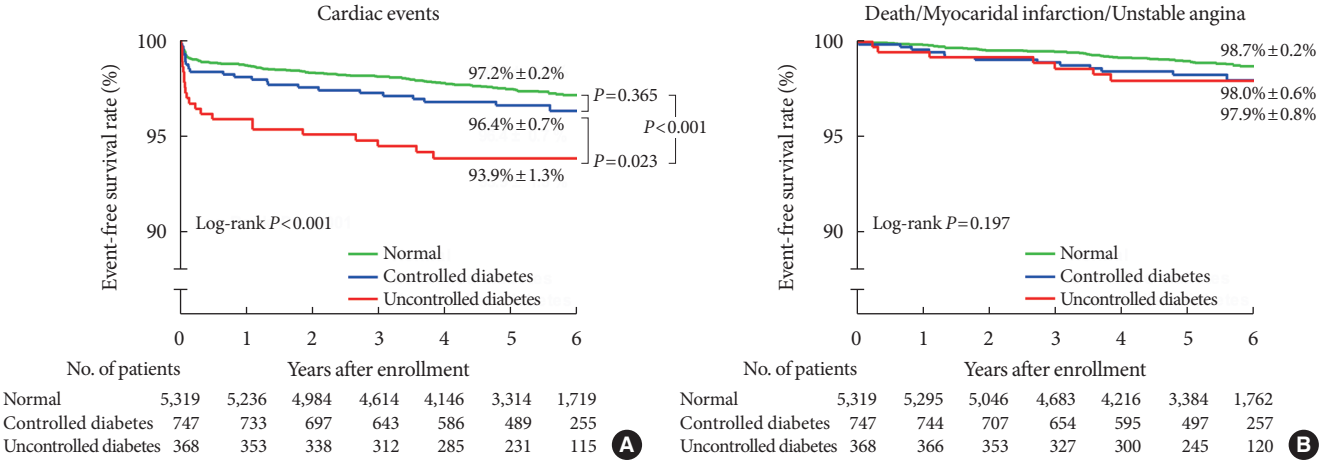

Fig. 1. Kaplan-Meier event-free survival curves of (A) 6-year cardiac events and (B) 6-year composite outcomes of all-cause death, myocardial infarction and unstable angina according to the diabetes control. The numbers in each figure represent the 6-year event-free survival rates.

consequently, uncontrolled diabetic individuals experienced more cardiac events; and (3) there findings suggest that diabetes control had a beneficial effect on the risk of subclinical coronary atherosclerosis in asymptomatic individuals.

In this study, uncontrolled diabetic individuals had a higher prevalence, extent, and severity of coronary atherosclerosis on CCTA than normal individuals. Even after adjustments for clinical and laboratory variables, uncontrolled diabetes was consistently associated with any subclinical coronary atherosclerosis. Moreover, uncontrolled diabetes was an independent risk factor for significant stenosis in the LM or proximal LAD, multi-vessel disease and high-risk CAD, which have been known to be associated with a worse prognosis [23]. As a result, uncontrolled diabetic individuals experienced more cardiac events. By contrast, compared with normal individuals, controlled diabetic individuals were not associated with the increased risk of significant subclinical coronary atherosclerosis (e.g., significant stenosis at least one coronary artery, signifi-

cant stenosis in the LM or proximal LAD, multi-vessel disease, or high-risk CAD). Consequently, cardiac event rates may have been comparable. Therefore, our findings support that diabetes control is important in preventing significant subclinical coronary atherosclerosis and cardiac events in asymptomatic diabetic individuals.

In earlier studies, intensive glucose control has not shown a significant effect on the rates of major cardiovascular events in diabetic patients [4,24]. However, long-term follow-up studies have demonstrated that early intensive glucose control may be effective in decreasing cardiovascular events in these patients [3,11]. A recent 15-year follow-up study also observed a significantly lower risk of major cardiovascular events during the periods of separation of the HbA1c curves [25]. Given that cardiac events are thought to occur after long periods of subclinical disease, our study provides some insights into these results. The current study showed that control of diabetes was associated with beneficial effects for significant subclinical coronary atherosclerosis which may have led to the differences in cardiac events between uncontrolled and controlled diabetic individuals. Therefore, in asymptomatic diabetic individuals, emphasis should be given on diabetes control to prevent future cardiac events.

To date, randomized trials have failed to demonstrate that routine screening for CAD can decrease cardiac events in relatively well-controlled asymptomatic diabetic populations [26,27]. In these trials, the study participants were treated by contemporary medical practice, achieving HbA1c, LDL-C, and systolic blood pressure levels at or near the target ranges (HbA1c 7.0% to 7.5%, LDL-C 86 to 114 mg/dL, and systolic blood pressure 129 to 133 mm Hg). Eventually, intensive intervention for current cardiac risk factors resulted in lower cardiac event rates in these patients. A previous study also demonstrated resolution of myocardial ischemia resulted from more aggressive treatment of cardiovascular risk factors [28]. In this present study, controlled diabetic individuals also had near targeted levels for HbA1c (6.2%), LDL-C (113 mg/dL), and systolic blood pressure (123 mm Hg). As a result, controlled diabetes was not associated with significant subclinical coronary atherosclerosis on CCTA and an increased risk of cardiac events. Since previous and our studies showed that the adherence to current guidelines could improve subclinical coronary atherosclerosis and clinical outcomes in asymptomatic diabetic individuals, further implementation of established guidelines is needed in this population.

Our study has several limitations. First, the current study was based in a single center. Moreover, because all study participants voluntarily went to the hospital for general health examination, there was a potential for selection bias. Second, since the present study is a retrospective cohort study, there was a limitation that these data did not fully reflect patient outcomes. Additionally, we did not specify the cause of death. Third, calcified plaques and higher coronary artery calcium score may lead to overestimation of significant coronary arteries stenosis. Fourth, our study population was almost Korean men. In addition, ethnic differences and clinical differences in diabetes have been noted between Asian and Western populations. Therefore, the generalization of our findings to female and other ethnic groups may be limited. Fifth, CCTA itself has limitations including radiation hazard, use of contrast, and higher cost. Although our study enrolled only volunteers, the use of CCTA in asymptomatic individuals has not yet been justified. Finally, we did not obtain the specific medical histories about diabetic duration, modalities of diabetic management, and antiplatelet agents, which could play an important role in potential confounders. Despite these limitations, we believe that the current study may have a clinical implication in unveiling an association between glycemic control and subclinical coronary atherosclerosis in asymptomatic individuals.

In this large observational study of asymptomatic individuals undergoing CCTA, uncontrolled diabetes was associated with significant subclinical coronary atherosclerosis and an increased risk for cardiac events. However, controlled diabetes did not associated with significant subclinical coronary atherosclerosis and an increase in cardiac events. These findings should be validated in additional studies.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2019.0073.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: G.M.P., C.H.L., S.W.L.

Acquisition, analysis, or interpretation of data: G.M.P., C.H.L., S.W.L., S.C.Y., Y.H.K., D.H.Y., J.W.K., T.H.L., H.K.K., J.C.
Drafting the work or revising: G.M.P., C.H.L., S.W.L., S.C.Y., Y.G.K., K.B.W., S.H.A., S.J.K., E.H.K., W.J.L., M.S.K., J.Y.P., S.G.L.
Final approval of the manuscript: G.M.P., C.H.L., S.W.L., S.C.Y., Y.H.K., Y.G.K., K.B.W., S.H.A., S.J.K., D.H.Y., J.W.K., T.H.L., E.H.K., W.J.L., M.S.K., J.Y.P., H.K.K., J.C., S.G.L.

ORCID

Gyung-Min Park *https://orcid.org/0000-0001-5846-0606*
Seung-Whan Lee *https://orcid.org/0000-0002-2662-5952*

ACKNOWLEDGMENTS

This research was supported by Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (2018R1D1A3B07043344).

REFERENCES

1. American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes. 2018. Diabetes Care 2018;41(Suppl 1):S55-64.
2. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, Rand L, Siebert C. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
3. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.
4. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129-39.
5. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72.
6. Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, Cuddihy R, Cushman WC, Genuth S, Grimm RH Jr, Hamilton BP, Hoogwerf B, Karl D, Katz L, Krikorian A, O'Connor P, Pop-Busui R, Schubart U, Simmons D, Taylor H, Thomas A, Weiss D, Hramiak I; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419-30.
7. Van Werkhoven JM, Cademartiri F, Seitun S, Maffei E, Palumbo A, Martini C, Tarantini G, Kroft LJ, de Roos A, Weustink AC, Jukema JW, Ardissino D, Mollet NR, Schuijf JD, Bax JJ. Diabetes: prognostic value of CT coronary angiography. Comparison with a nondiabetic population. Radiology 2010;256:83-92.
8. Hadamitzky M, Hein F, Meyer T, Bischoff B, Martinoff S, Schomig A, Hausleiter J. Prognostic value of coronary computed tomographic angiography in diabetic patients without known coronary artery disease. Diabetes Care 2010;33:1358-63.
9. Rana JS, Dunning A, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng VY, Chinnaiyan K, Chow BJ, Cury R, Delago A, Feuchtner G, Hadamitzky M, Hausleiter J, Kaufmann P, Karlsberg RP, Kim YJ, Leipsic J, Labounty TM, Lin FY, Maffei E, Raff G, Villines TC, Shaw LJ, Berman DS, Min JK. Differences in prevalence, extent, severity, and prognosis of coronary artery disease among patients with and without diabetes undergoing coronary computed tomography angiography: results from 10,110 individuals from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes): an InteRnational Multicenter Registry. Diabetes Care 2012;35:1787-94.
10. Hammoud T, Tanguay JF, Bourassa MG. Management of coronary artery disease: therapeutic options in patients with diabetes. J Am Coll Cardiol 2000;36:355-65.
11. Writing Group for the DCCT/EDIC Research Group, Orchard TJ, Nathan DM, Zinman B, Cleary P, Brillon D, Backlund JY, Lachin JM. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. JAMA 2015;313:45-53.
12. Park GM, Yun SC, Cho YR, Gil EH, Her SH, Kim SH, Jo MW, Lee MS, Lee SW, Kim YH, Yang DH, Kang JW, Lim TH, Kim BJ, Koh JM, Kim HK, Choe J, Park SW, Park SJ. Prevalence of coronary atherosclerosis in an Asian population: findings from coronary computed tomographic angiography. Int J Cardiovasc Imaging 2015;31:659-68.

13. Park GM, Han S, Kim SH, Jo MW, Her SH, Lee JB, Lee MS, Kim HC, Ahn JM, Lee SW, Kim YH, Kim BJ, Koh JM, Kim HK, Choe J, Park SW, Park SJ. Model for assessing cardiovascular risk in a Korean population. Circ Cardiovasc Qual Outcomes 2014;7:944-51.
14. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes. 2018. Diabetes Care 2018;41(Suppl 1):S13-27.
15. Jung CH, Lee MJ, Hwang JY, Jang JE, Leem J, Park JY, Lee J, Kim HK, Lee WJ. Elevated serum ferritin level is associated with the incident type 2 diabetes in healthy Korean men: a 4 year longitudinal study. PLoS One 2013;8:e75250.
16. Raff GL, Abidov A, Achenbach S, Berman DS, Boxt LM, Budoff MJ, Cheng V, DeFrance T, Hellinger JC, Karlsberg RP; Society of Cardiovascular Computed Tomography. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. J Cardiovasc Comput Tomogr 2009;3:122-36.
17. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827-32.
18. Leber AW, Becker A, Knez A, von Ziegler F, Sirol M, Nikolaou K, Ohnesorge B, Fayad ZA, Becker CR, Reiser M, Steinbeck G, Boekstegers P. Accuracy of 64-slice computed tomography to classify and quantify plaque volumes in the proximal coronary system: a comparative study using intravascular ultrasound. J Am Coll Cardiol 2006;47:672-7.
19. Hausleiter J, Meyer T, Hadamitzky M, Kastrati A, Martinoff S, Schomig A. Prevalence of noncalcified coronary plaques by 64-slice computed tomography in patients with an intermediate risk for significant coronary artery disease. J Am Coll Cardiol 2006;48:312-8.
20. Min JK, Shaw LJ, Devereux RB, Okin PM, Weinsaft JW, Russo DJ, Lippolis NJ, Berman DS, Callister TQ. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J Am Coll Cardiol 2007;50:1161-70.
21. Min JK, Berman DS, Dunning A, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng V, Chinnaiyan K, Chow BJ, Cury R, Delago A, Feuchtner G, Hadamitzky M, Hausleiter J, Kaufmann P, Karlsberg RP, Kim YJ, Leipsic J, Lin FY, Maffei E, Plank F, Raff G, Villines T, Labounty TM, Shaw LJ. All-cause mortality benefit of coronary revascularization vs. medical therapy in patients without known coronary artery disease undergoing coronary computed tomographic angiography: results from CONFIRM (COronary CT Angiography EvaluatioN for Clinical Outcomes: an InteRnational Multicenter Registry). Eur Heart J 2012;33:3088-97.
22. BARI 2D Study Group, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, Orchard TJ, Chaitman BR, Genuth SM, Goldberg SH, Hlatky MA, Jones TL, Molitch ME, Nesto RW, Sako EY, Sobel BE. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009;360:2503-15.
23. Park GM, Lee JH, Lee SW, Yun SC, Kim YH, Cho YR, Gil EH, Kim TS, Kim CJ, Cho JS, Park MW, Her SH, Yang DH, Kang JW, Lim TH, Koh EH, Lee WJ, Kim MS, Lee KU, Kim HK, Choe J, Park JY. Comparison of coronary computed tomographic angiographic findings in asymptomatic subjects with versus without diabetes mellitus. Am J Cardiol 2015;116:372-8.
24. 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.
25. Reaven PD, Emanuele NV, Wiitala WL, Bahn GD, Reda DJ, McCarren M, Duckworth WC, Hayward RA; VADT Investigators. Intensive glucose control in patients with type 2 diabetes: 15-year follow-up. N Engl J Med 2019;380:2215-24.
26. Young LH, Wackers FJ, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Heller GV, Iskandrian AE, Wittlin SD, Filipchuk N, Ratner RE, Inzucchi SE; DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study. A randomized controlled trial. JAMA 2009;301:1547-55.
27. Muhlestein JB, Lappe DL, Lima JA, Rosen BD, May HT, Knight S, Bluemke DA, Towner SR, Le V, Bair TL, Vavere AL, Anderson JL. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. JAMA 2014;312:2234-43.
28. Wackers FJ, Chyun DA, Young LH, Heller GV, Iskandrian AE, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Filipchuk N, Ratner RE, Inzucchi SE; Detection of Ischemia in Asymptomatic Diabetics (DIAD) Investigators. Resolution of asymptomatic myocardial ischemia in patients with type 2 diabetes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. Diabetes Care 2007;30:2892-8.