Presence, Characteristics, and Volumes of Coronary Plaque Determined by Computed Tomography Angiography in Young Type 2 Diabetes Mellitus

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Prevention and management of coronary artery disease (CAD) is of great concern in patients with diabetes mellitus. Although the impact of coronary atherosclerosis is described well for subjects older than 40 years, the prevalence and types of coronary atherosclerosis in young patients are not well known. The aim of this study was to evaluate the prevalence, extent, severity, and volumes of coronary plaque in type 2 diabetes mellitus (T2DM) population younger than of 40 years. This prospective study enrolled 181 subjects (25-40 year old) undergoing coronary computed tomography angiography, with 86 T2DM and 95 nondiabetic age/gender-matched subjects. Coronary artery calcium (CAC), plaque assessment including total segment stenosis (sum of individual segmental stenosis), total plaque scores (sum of semiquantitative segmental plaque burden), segment involvement scores (number of segments with plaque) were evaluated. In addition, we quantitatively measured plaque volumes in total, fibrous, fibrous fatty, dense calcified, and low-attenuation plaque using novel plaque software. Compared with nondiabetic patients, the prevalence of CAD, calcified, and noncalcified plaques was higher in patients with T2DM (19% vs 58%; p <0.001). In patients with a zero CAC, T2DM had a higher prevalence (46%) of noncalcified plaque (p <0.0001). In multivariate linear regression models after adjusting for traditional cardiovascular risk factors, increased total segmental stenosis, total plaque scores, and segment involvement scores were associated with T2DM. Regarding quantitative plaque assessment, all volumes in noncalcified plaque type were approximately threefold higher in patients with T2DM. In conclusion, young patients with T2DM are susceptible to premature CAD with more calcified and noncalcified plaques. Early prevention program using computed tomography angiography might be helpful in identifying young diabetic patients with subclinical atherosclerosis. **(Am J Cardiol 2017;■:■−■)**

Coronary artery disease (CAD) is the most common complication and the principal cause of death in type 2 diabetes mellitus (T2DM).[1] Before developing clinical evidence of CAD, asymptomatic atherosclerosis has been presented for years and even decades.[2,3] Identification and early management of cardiovascular risk are essential and has been shown to prevent morbidity and mortality associated with CVD in subjects with or without diabetes.[4−6] There is a reluctance to start medications in younger diabetic patients as many are believed to have little or no atherosclerosis until later in life or due to the longer duration of their diabetes. Several studies have demonstrated that younger patients with T2DM have an increased CVD risk,[7−9] but its prevalence is not well known. We conducted this study to find the prevalence of subclinical coronary atherosclerosis, Coronary artery calcium (CAC), and plaque characteristics using low-dose protocol computed tomography angiography in young subjects with T2DM and compared them with those of the same age and gender in the nondiabetic population.

Methods

This study was a prospective case-control study performed at the Clinical and Translational Research Center at Los Angeles Biomedical Research Institute (Torrance, California) from September 2012 to September 2015. All participants underwent CAC scanning and coronary computed tomography angiography (CCTA) to evaluate early coronary atherosclerotic disease. Based on pilot study,[7] we enrolled 181 subjects included 86 young patients

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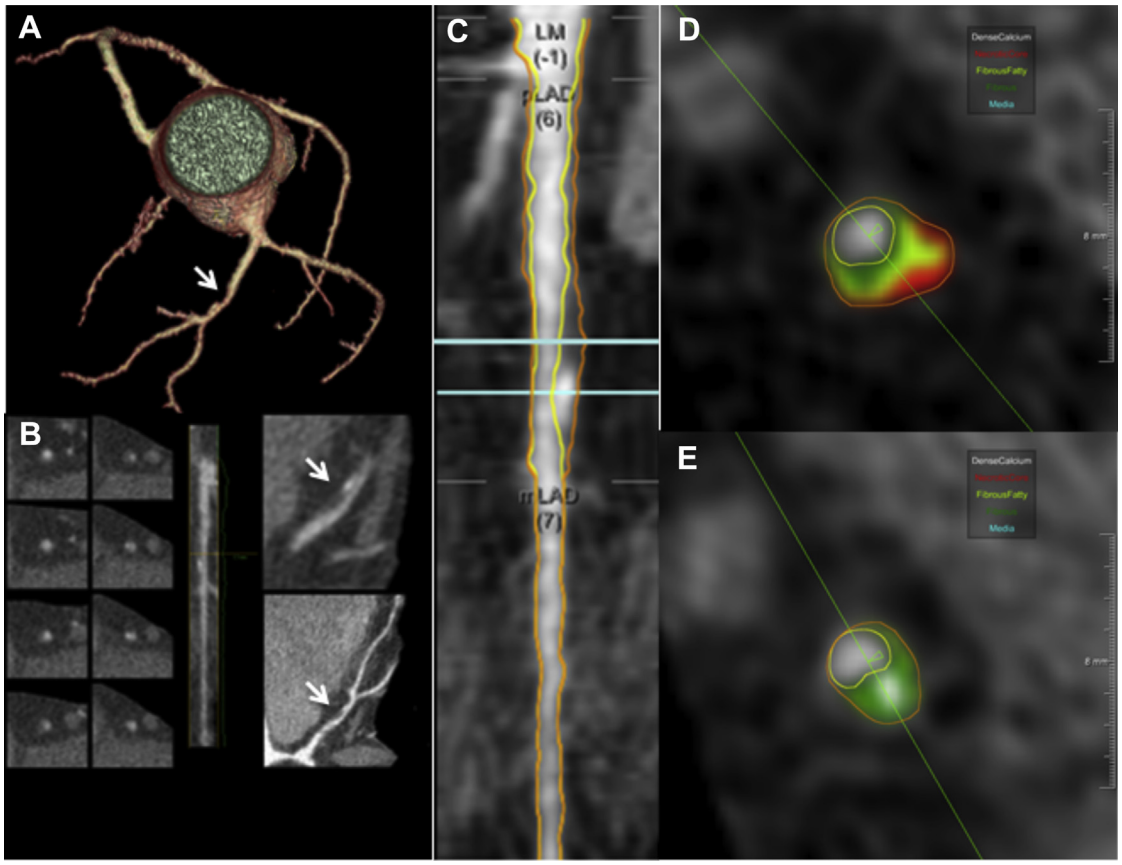

Figure 1. A 35-year-old man with a 4-year history of diabetes. *(A)* Volume rendering of the coronary tree. *(B)* Cross-sectional and curved multiplanar reconstruction of the LAD shows mixed, noncalcified, and calcified coronary plaque *(arrow)*. Coronary segmentation model and quantitative measurement of different plaque types *(C, D,* and *E)*. Dense calcium: *white*; necrotic core or low-attenuation plaque: *red*; fibrous fatty: *light green*; fibrous: *dark green*. LAD = left anterior descending artery; LM = left main; mLAD = mid left anterior descending artery; pLAD = proximal left anterior descending artery.

(25 to 40 years old) with a minimum of 5-year history of T2DM from the endocrinology clinic and 95 age/gender-matched asymptomatic subjects by invitation and call as a control group. After obtaining informed consent from all patients, detailed information about the individual's health status was recorded, and fasting blood samples were drawn for plasma glucose, lipid profile, and hemoglobin A1C. Patients with abnormal renal function (creatinine >1.5), history of congenital heart disease, weighing more than 300 pounds, pregnant, or known allergies to the contrast solution were excluded. Female subjects had a urine pregnancy test done at the beginning of the visit. This study was approved by the Institutional Review Board of Los Angeles Biomedical Institute at Harbor UCLA Medical Center.

CCTA was performed with a 64-slice GE Scanner (VCT; GE Inc., Milwaukee, Wisconsin). β blocker was used for reducing heart rates to below 65 beats/min. All patients received 0.4 mg of sublingual nitroglycerin 1 minute before their scan, unless they had a blood pressure less than 90 mm Hg or they took phosphodiesterase 5 inhibitors within 24 hours of the study. The examination was performed in 2 phases. In the first phase, noncontrast computed tomography scanning was done to generate a CAC score. In the second phase, 50 to 90 ml of (dependent on body mass index) intravenous iodinated isoosmolar, nonionic contrast (Visipaque; GE Healthcare, Milwaukee, Wisconsin) was administered. A prospective electrocardiogram-triggered, contrast-enhanced CTA was performed based on previously reported protocols.[7,10] The scan parameters were 64 × 0.625-mm collimation and 80- to 120-mV tube voltage, and mean effective mA (adjusted depending on body habitus) was 604 mA.

The raw data were reconstructed, and the images were evaluated in blinded fashion on a 3-dimensional image analyzing workstation (GE Advantage Workstation; GE Healthcare) by an expert reader. Coronary analysis included a calculated calcium score, stenosis percentage, and measured plaque types for each patient using a 17-segment American Heart Association (AHA) coronary artery model.[11] We categorized each stenotic segment as normal (no stenosis), 1% to 29%, 30% to 49%, 50% to 69%, and ≥ 70% stenosis using a visual semiquantified method and categorized them using a score of 0 to 4, respectively. Total stenosis segments and segment involvement scores were also calculated.[7] Significant stenosis was defined as atleast 50% luminal narrowing. Plaque burden severity was evaluated for each individual segment and scored as a 0 (no plaque), 1 (mild coronary plaque), 2 (moderate coronary plaque), or 3 (severe coronary plaque). Total plaques score (sum of semiquantitative segmental plaque burden or total plaque scores) were calculated for each individual.[7]

Table 1
The distribution of study participant characteristics, stratified by diabetes status

Variable	Diabetes Mellitus		*p*-value
	No (n = 95)	Yes (n = 86)	
Age (years)	30-38 (median 34)	32- 39 (median 36)	0.059
Female	44(46%)	48(56%)	0.202
White (non-Hispanic)	35(38%)	53(62%)	<0.001***
Black (non-Hispanic)	5(5%)	15(17%)	
Hispanic	25(27%)	14(16%)	
Asian	28(30%)	4(5%)	
Body Mass Index (kg/m^2)	25.0- 30.8 (median 28.7)	28.1- 38.9 (median 33.3)	<0.001***
Smoking			0.233
Never	76(80%)	60(70%)	
Current	12(13%)	14(16%)	
Past	7(7%)	12(14%)	
Hypertension	7(7%)	25(29%)	<0.001***
Systolic Blood Pressure (mm Hg)	116 (107, 125)	119 (109, 126)	0.292
Diastolic Blood Pressure (mm Hg)	70 (67, 80)	74 (70, 80)	0.213
Dyslipidemia	3(3.2%)	43(50.0%)	<0.001***
Family History of CAD	46(48.4%)	68(79.1%)	<0.001***
Duration of Diabetes (year)	0	8- 15 (median 11)	
Insulin Consumption	0 (0%)	50(58%)	
Agatston score[†]			0.001**
0	83(88%)	56(67%)	
1-100	10(11%)	20(24%)	
101-400	0(0%)	5(6%)	
>400	1(1%)	2(2%)	
HbA1C	5.1-5.7 (median 5.4)	7.5-10.8 (median 8.6)	<0.001***
HDL Cholesterol (mg/dL)	35-48 (median 41)	36-50 (median 43)	0.312
Total Cholesterol (mg/dL)	116-164 (median142)	131-192 (median159)	0.003**
Triglycerides (mg/dL)	69- 131 (median 97)	100-191 (median138)	<0.001***

Continuous data are presented as median (interquartile), and categorical data are presented as no (%) of patients, unless otherwise indicated.
CAD = coronary artery disease; GFR = glomerular filtration rate; HbA1C = hemoglobin A1C; HDL = high density lipoprotein.
*p <0.05.
**p <0.01.
***p <0.001.
[†] Fisher's exact test was performed.

Semiautomated quantitative CTA was performed per coronary artery segment[11] using QAngio CT software (Research Edition, version 2.1.2; Medis medical imaging systems, Leiden, the Netherlands) as described in previous studies (Figure 1).[12] We excluded vessels with a diameter <1.5 mm. Seven images with severe motion and noise were excluded. Coronary plaque volume, including total plaque volume (TPV), total plaque burden (TPV per segment's length), fibrotic, fibro-fatty, low-attenuation plaque, and dense calcium volumes were acquired using predefined Hounsfield unit thresholds.[13,14] Manual corrections were made and confirmed by 2 expert readers. Reproducibility for using the software has been reported previously.[15,16]

Baseline characteristics of the study population were analyzed in the diabetic and nondiabetic population. All the categorical variables were calculated as frequency (percentage), and continuous data were presented as median (interquartile range) due to lack of normal distribution for most variables. For comparisons of risk factors between nondiabetic and diabetic patients, we used the Mann-Whitney *U* test and chi-square test. TPV, total plaque burden, and plaque volumes of different characteristics were categorized into tertiles. A relative risk (RR) regression model was developed, and RRs were used to evaluate the association between diabetes and coronary plaque volume, stenosis scores, and CAC score prevalence. Further adjustments were performed as covariates age, gender, ethnicity, body mass index, hypertension, hyperlipidemia, smoking condition, and family history of CAD were entered into the model based on their potential roles as confounders. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina), and statistical significance levels of all the analysis were set at p = 0.05 (2 sided).

Results

Among 181 recruited subjects, age and gender were similar by design in the T2DM and nondiabetic populations. The prevalence of subclinical CAD in young diabetic subjects was 58% compared with 20% in nondiabetic group (p <0.001). The median duration of diabetes was 11 (8 to 15) years. Except for smoking history, the presence of the traditional risk factors for CAD was significantly higher in patients with diabetes (Table 1). Almost all of our total population (98.9%) had an American College of Cardiology (ACC)/AHA risk score[17] less than 10%.

Young T2DM had about a 25% risk of getting CAC compared with nondiabetic participants (RR 1.253, 95% CI

Table 2
The coronary plaque characteristics, semiquantitative plaque volume, and coronary stenosis, stratified by diabetes status

Variable	Diabetes Mellitus		p-value
	No (n = 95)	Yes (n = 86)	
Significant Stenosis[†]	1(1%)	6(7%)	0.054
Plaque type			<0.001***
No plaque	73(80%)	34(41%)	
Non-calcified	11(12%)	23(28%)	
Calcified-mixed	7(8%)	26(31%)	
Total Plaque Volume (mm^3)	0 (mean 0)	0-66.3 (mean 12.63)	<0.001***
Total Plaque Volume > 0	19(20%)	50(58%)	<0.001***
Plaque Segments Included			<0.001***
0	76(80%)	36(42%)	
1	14(15%)	22(28%)	
2+	5(5%)	21(27%)	
Dense Calcium Volume (mm^3)	0	0- 2.6 (mean 0)	<0.001***
Dense Calcium Volume > 0	10(10.5%)	33(42%)	<0.001***
Fibrous Fatty Volume (mm^3)	0	0 - 15.9 (mean 1.1)	<0.001***
Fibrous Fatty Volume > 0	19(20%)	43(54%)	<0.001***
Fibrous Volume (mm^3)	0	0 - 54.5 (mean 8.1)	<0.001***
Fibrous Volume > 0	19(20%)	43(54%)	<0.001***
Low Attenuation Volume (mm^3)	0	0 - 4.2 (mean 0.28)	<0.001***
Low Attenuation Volume > 0	19(20%)	42(53%)	<0.001***

Continuous data are presented as median (interquartile), and categorical data are presented as no. (%) of patients, unless otherwise indicated.
*p <0.05.
**p <0.01.
***p <0.001.
[†] Significant stenosis is defined as luminal narrowing more than 50%.

1.049 to 1.497, p = 0.013) after adjustment of age, gender, race, body mass index, smoking condition, hypertension, hyperlipidemia, and family history of CAD. All types of atherosclerotic plaque appeared more frequently in young patients with T2DM (Table 2). Total plaque burden was significantly higher in young T2DM subjects with the RR of 2.887 (95% CI 1.562 to 5.336; p <0.001) after adjustment for traditional risk factors. Moreover, fibrous, fibrous fatty, low-attenuation, and dense calcium plaque volumes were significantly greater even after adjusting for risk factors (Table 3). Contribution-based priority assessment for age and duration of DM in the progression of coronary atherosclerosis showed the age of 25.2 years is a cut-off point for having any coronary plaque in this study population (area under the curve = 0.721, p <0.01).

Discussion

Although patients with diabetes are susceptible to vascular complications and more specifically, coronary atherosclerosis,[18] there are few observational studies that show the prevalence of CAD in young T2DM. In a study on 1,635

Table 3
Relative risk ratio (RR) and 95% CI of coronary plaque volumes in T2DM

Variable	Unadjusted Model		Adjusted Model	
	RR (95%CI)	p-value	RR (95%CI)	p-value
Total Plaque Volume	3.271 (2.012, 5.319)	<0.001***	3.442 (1.943, 6.096)	<0.001***
Dense Calcium Volume	4.381 (2.206, 8.699)	<0.001***	5.645 (2.492, 12.791)	<0.001***
Fibrous Fatty Volume	3.099 (1.905, 5.041)	<0.001***	3.300 (1.822, 5.978)	<0.001***
Fibrous Volume	3.271 (2.012, 5.319)	<0.001***	3.380 (1.907, 5.991)	<0.001***
Low Attenuation Volume	2.612 (1.607, 4.248)	<0.001***	2.878 (1.570, 5.276)	<0.001***
TSS score	3.380 (1.627, 7.021)	0.001**	3.441 (1.475, 8.028)	0.004**
TPS score	3.419 (1.681, 6.952)	<0.001***	3.712 (1.647, 8.364)	0.002**
SIS score	3.139 (1.659, 5.938)	<0.001***	3.047 (1.398, 6.637)	0.005**
CAC score	1.260 (1.104, 1.436)	<0.001***	1.253 (1.049, 1.497)	0.013*
Any Plaque	2.907 (1.872, 4.515)	<0.001***	2.715 (1.560, 4.727)	<0.001***

The model adjusted for age, gender, race, BMI, smoking condition, hypertension, hyperlipidemia, and family history of CAD.
SIS = segment involvement score; TPS = total plaque score; TSS = total stenosis score.
*p <0.05.
**p <0.01.
***p <0.001.

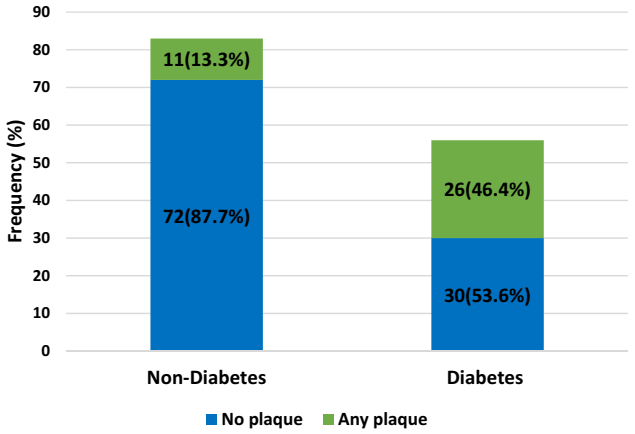

Figure 2. Plaque composition in participants with no coronary calcifications using the Agatston Score in the nondiabetic population (n = 83) and the young T2DM group (n = 56). Almost half of the diabetic patients with zero Agatston score had evidence of atherosclerotic plaque.

young subjects undergoing coronary CTA from the registry, diabetes was a strong predictor of having any coronary plaque among the asymptomatic population (odds ratio 3.31, 95% CI 1.19 to 9.21, p = 0.02).[8] We previously found a 57.5% prevalence of CAD detected by computed tomography in a cross-sectional small study on 40 young DM.[7] In the present study, we showed the similarity of the presence of CAD among young patients with T2DM, which was significantly greater than patients without diabetes even after adjusting for classical risk factors (58% vs 20%). These studies have also demonstrated that young patients with T2DM had more noncalcified plaque compared with nondiabetic patients. The results of our study expand on these findings by demonstrating the consistent associations between T2DM and the large prevalence of noncalcified plaque. The strength of the present study is that we quantitatively measured volumes of the detailed noncalcified plaque components such as fibrous, fibrous fatty, and low-attenuation plaque. Our study is the first study comparing each noncalcified plaque volume between patients with and without T2DM and showed that the volume of any noncalcified plaque component was significantly higher in young T2DM patients than that in nondiabetic patients (Tables 2 and 3).

Several studies have reported subclinical CAC in the asymptomatic diabetic population.[19–22] In our population, CAC was significantly higher in the diabetic group indicating that calcium scanning is useful in the early detection of CAD among young subjects with T2DM. However, a significant amount of young patients with noncalcified plaque may be neglected. Several studies showed that zero CAC could not rule out the presence of CAD.[23,24] In our population with a zero Agatston score, diabetic patients had a threefold higher prevalence of noncalcified plaque compared with nondiabetic patients (Figure 2).

The new ACC/AHA lipid guidelines on standards of medical care in diabetes emphasize the importance of cardiovascular risk factors in the management of diabetes for those aged <40 years.[25] In our low AHA/ACC risk score population, the presences of traditional cardiovascular risk factors were higher in young T2DM; however, our results showed that CAC and coronary plaque were more prevalent in the diabetic population even after adjustment of these risk factors suggesting that CCTA can be additional tools to risk stratify the young patients with T2DM for cardiovascular risk. Although several studies have rejected the theory of equivalency of diabetes with CAD,[26] diabetes is introduced as a complex chronic illness, and we could not ignore the major impact of diabetes to the cardiovascular system.[27,28] There are no adequate data for the management of young T2DM in the current guidelines. The cut point for presenting the coronary atherosclerosis in our study was 25.2 years and we highly suggest using noninvasive CCTA in young T2DM and more longitudinal outcome studies to prove the benefit of medical anti atherosclerotic treatment in this population.

Lack of information on the younger diabetic population may be partly due to the uneasy justification of invasive procedures and radiation exposure. However, radiation doses have dramatically decreased through the use of novel technology. Radiation levels less than 3 mSv can be achieved now, which equates to 1 year of background radiation.[29,30] In this current noninvasive and low-dose radiation study with median 1.8 mSv, we effectively found that patients with T2DM had larger prevalence of coronary atherosclerosis including both noncalcified and calcified plaque. Since CTA and quantitative plaque measurements are able to provide much detailed information, we can consider them as sensitive tools for a more precise cardiovascular risk evaluation and earlier medical therapy of higher risk populations with T2DM.

There are some limitations in the present study. We enrolled patients with T2DM based on clinical records and questionnaires. We are reasonably certain that the vast majority of patients had T2DM, but we did not perform additional testing to exclude cases with type 1 DM. In addition, low-density lipoprotein was calculated using the Friedewald equation. We could not rely on low-density lipoprotein measurement as a risk factor; therefore, history of hyperlipidemia and lipid-lowering drugs consumption obtained from medical records was used.

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Disclosures

The authors have no conflicts of interest to disclose.

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