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# Plaque progression assessed by a novel semi-automated quantitative plaque software on coronary computed tomography angiography between diabetes and non-diabetes patients: A propensity-score matching study



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## ABSTRACT

**Background and aims:** We aimed at investigating whether diabetes is associated with progression in coronary plaque components.

**Methods:** We identified 142 study subjects undergoing serial coronary computed tomography angiography. The resulting propensity score was applied 1:1 to match diabetic patients to non-diabetic patients for clinical risk factors, prior coronary stenting, coronary artery calcium (CAC) score and the serial scan interval, resulting in the 71 diabetes and 71 non-diabetes patients. Coronary plaque (total, calcified, non-calcified including fibrous, fibrous-fatty and low attenuation plaque [LAP]) volume normalized by total coronary artery length was measured using semi-automated plaque software and its change overtime between diabetic and non-diabetic patients was evaluated.

**Results:** The matching was successful without significant differences between the two groups in all matched variables. The baseline volumes in each plaque also did not differ. During a mean scan interval of  $3.4 \pm 1.8$  years, diabetic patients showed a 2-fold greater progression in normalized total plaque volume (TPV) than non-diabetes patients ( $52.8 \text{ mm}^3$  vs.  $118.3 \text{ mm}^3$ ,  $p = 0.005$ ). Multivariable linear regression model revealed that diabetes was associated with normalized TPV progression ( $\beta$  72.3, 95%CI 24.3–120.3). A similar trend was observed for the non-calcified components, but not calcified plaque ( $\beta$  3.8, 95%CI –27.0–34.7). Higher baseline CAC score was found to be associated with total, non-calcified and calcified plaque progression. However, baseline non-calcified volume but not CAC score was associated with LAP progression.

**Conclusions:** The current study among matched patients indicates diabetes is associated with a greater plaque progression. Our results show the need for strict adherence of diabetic patients to the current preventive guidelines.

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## 1. Introduction

Diabetes mellitus is a well-known risk factor for coronary artery disease (CAD). In the U.S., almost 18.8 million individuals had experienced diabetes and its prevalence has increased among all

age groups [1]. In a recent large cohort study of >2,500,000 individuals, the risk in cardiovascular mortality among diabetes patients was 2- to 3-fold higher compared to young or middle aged non-diabetic subjects, and cardiovascular disease (CVD) was a major contributing factor for death [2]. Diabetes has been considered as a CAD equivalent, thus current guidelines recommend intensive medical therapy for both primary and secondary prevention [3,4].

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Given the high risk nature of diabetes, traditional non-invasive functional tests are appropriate to use to identify risk among diabetes patients [5,6]. However, despite normal findings of functional tests, diabetes patients were found to experience more cardiac events compared to non-diabetes patients [7–9]. These observations were also confirmed in a recent investigation by Valenti et al., demonstrating that a coronary artery calcium (CAC) score of zero could no longer predict all-cause death beyond 5 years among diabetes patients [10]. The data represents a much shorter warranty period of a “normal” CAC score than that of >10 years for a general asymptomatic population [11,12]. These findings potentially highlight the important fact that diabetes was likely to be associated with advanced coronary atherosclerosis, but which may not be functionally significant or visualized on non-contrast CT, yet much more accumulated overtime, active to rapid plaque progression or rapid progress of ischemia [13].

Coronary computed tomography angiography (CCTA) has emerged to assess the presence, extent and severity of CAD and evaluate future CVD risk among individuals with various risk factors [14–16]. Besides, coronary plaque progression has been acknowledged to be associated with CVD events by recent investigations using CCTA [17]. In this study, we investigated whether diabetes patients experience a greater plaque progression compared to non-diabetic patients.

## 2. Materials and methods

### 2.1. Study population

Among 678 patients who were clinically referred for serial coronary computed tomographic angiography (CCTA) between September 2006 and November 2015 at Harbor UCLA Medical Center (Torrance, California, USA), we identified 143 patients with diabetes. Because of the potential differences in the baseline clinical factors, the resulting propensity score was applied 1:1 to match diabetic subjects to non-diabetic subjects for age, gender, hypertension, dyslipidemia, current smoking and family history of CAD, history of percutaneous coronary intervention (PCI), baseline coronary artery calcium (CAC) score and scan interval between baseline and follow-up. We matched these confounding factors between patients with and without diabetes in order to detect the pure effect of diabetes on plaque progression. The matching resulted in 142 patients with 71 diabetic and 71 non-diabetic patients. Patients with a history of coronary bypass, coronary revascularization between baseline and follow-up or a <1 year interval between the baseline and follow-up scans were excluded. Diabetes was defined as diagnosis by physician or the use of oral anti-diabetes medications or insulin. Other CAD risk factors were defined as previously reported [18]. This study was approved by the Institutional Review Board of our institution (Los Angeles BioMedical Institute at Harbor UCLA Medical Center, Torrance, California, USA).

### 2.2. Non-contrast CT image acquisition and CCTA image acquisition protocols

All patients were scanned using a 64-slice CT scanner (Light-speed VCT, General Electric Healthcare, Milwaukee, Wisconsin) and underwent non-contrast CT for CAC before CCTA scanning. Each scan extended from 1 cm below the carina to the bottom of the heart to include the entire coronary tree. Scan parameters included as follows: prospective electrocardiogram-triggering (65–80%), 35 cm field-of-view, 512 × 512 matrix size, and peak tube voltage of 120 kVp. Slice thickness was 3 mm. CAC measurements were performed on a dedicated workstation (AW Volume Share™, GE

Medical Systems, Milwaukee, WI), and CAC was quantified using the Agatston score [19].

With respect to CCTA image, scanning parameters were as follows: typically 70%–80% of the R-R interval for prospective electrocardiogram-triggering and 35%–80% for retrospective study, collimation 64 × 0.625 mm, tube voltage 100 kV–120 kV, tube current 350–780 mA. Pre-scan oral and/or intravenous beta-blocker was administered to reach target heart rate <60 beats/min (bpm). Immediately before scanning, sublingual nitroglycerin or nitroglycerin spray 0.4–0.8 mg was administered.

Experienced readers evaluated CCTAs for the presence and volume of coronary plaques using semi-automated plaque analysis software (QAngioCT Research Edition version 2.1.2, Medis medical imaging systems bv, Leiden, The Netherlands). According to a modified 17-segment American Heart Association coronary tree model, detected plaques were allocated according to plaque location [20]. The software automatically extracted centerlines and performed automated detection of the inner lumen and vessel wall contours from the ostium to the distal end of each artery in straightened the multiplanar reformatted images. When required, we manually modified the contours for the coronary lumen or vessel. As previously reported, window level and width were set at 740 and 220 Hounsfield units (HU) to visualize the lumen, vessel and plaque [21]. Vessel and plaque volumes were measured in segments with sufficient image quality and ≥1.5 mm in lumen diameter. We previously reported that good correlations were observed with respect to the total plaque volume measurement between two observers (Correlation coefficient 0.94, 95% CI 0.80–0.98) [22]. Vessel length was defined as the length of coronary arteries in measured total segments. Segments with stents were excluded. Since the attenuation of coronary plaque is influenced by lumen contrast intensity, coronary plaque including non-calcified plaque (fibrous, fibrous-fatty and low attenuation plaque [LAP]) and calcified plaque was defined based upon densities in plaques, which were adapted to lumen contrast intensity as previously described [23].

Coronary plaque, vessel and lumen volumes at baseline and follow-up were measured and plaque change over time between diabetic and non-diabetic patients was evaluated.

### 2.3. Statistical analysis

This study was a propensity-matched study, in which each diabetic patient was matched to non-diabetic patient by age, gender, hypertension, dyslipidemia, current smoking and family history of CAD, history of percutaneous coronary intervention (PCI), baseline coronary artery calcium (CAC) score and scan interval between baseline and follow-up. Plaque progression was analyzed in the group matched for these variables using propensity scores, where the propensity score was the resulting predicted probabilities of a logistic regression model predicting being in the two groups with these confounders as the predictors. The propensity score was applied 1:1 to match between the two groups using optimal matching algorithm [24].

All analyses of CCTA variables were performed independently to the clinical characteristics. A Student's t-test is used to compare variables where the variable a normal distribution or the Mann-Whitney *U* test for non-parametrically distributed variables between baseline and follow-up groups. Each plaque volume was derived from [vessel volume – lumen volumes (mm<sup>3</sup>)] at baseline and follow-up. Normalized plaque volume was calculated [(plaque volume/total length of measured coronary arteries) multiplied by mean total length for all studies] [21]. Changes in plaque volume were estimated as the difference of volumes between baseline and follow-up.

Multivariate linear regression models were conducted to determine whether diabetes is associated with each plaque progression after adjusting for age, gender, hypertension, dyslipidemia, current smoking and family history of CAD, prior PCI, aspirin use, statin use, the scan interval years between baseline and follow-up and baseline coronary artery calcium (CAC) score (log of the CAC score [logCAC]) or baseline normalized non-calcified plaque volume. Median normalized plaque volume [PV] changes in each type of plaque were compared between non-diabetes and diabetes groups by CAC categories with 0, 1–399 and  $\geq 400$ .  $p$ -values  $< 0.05$  were considered statistically significant. All statistical analyses were performed using SAS software (version 9.3 SAS institute, Cary, North Carolina). Sample size to detect a 50 mm<sup>3</sup> difference (mean total plaque volume [TPV] progression) between the groups was with 80% power and  $\alpha = 0.05$  was 63 subjects in per group.

### 3. Results

Table 1 shows the patient baseline characteristics. The matching was successful without significant differences between the diabetic and non-diabetic groups, in all variables considered for the matching ( $p > 0.05$ ) (Table 1). Four patients had a history of myocardial infarction (MI) in the non-diabetes group, whereas no MI was observed in the diabetic group. Diabetes patients were more often treated with aspirin (16.9% vs. 5.6%,  $p = 0.03$ ) and statin (49.3% vs. 26.8%,  $p = 0.006$ ) compared to non-diabetes patients. Fifty-eight patients had lipid measurements at baseline. Total cholesterol ( $176.3 \pm 9.4$  mg/dl vs.  $163.4 \pm 6.8$  mg/dl,  $p = 0.37$ ) and low density lipoprotein ( $97.4 \pm 8.3$  mg/dl vs.  $85.7 \pm 5.5$  mg/dl,  $p = 0.24$ ), which were not matched previously, were shown to be slightly higher in the non-diabetes group than the diabetes group, whereas they were not statistically different. Other non-matched variables including levels of high density lipoprotein ( $51.4 \pm 3.0$  mg/dl vs.  $50.0 \pm 3.1$  mg/dl,  $p = 0.71$ ), triglycerides ( $127.9 \pm 12.7$  mg/dl vs.  $144.6 \pm 20.1$  mg/dl,  $p = 0.49$ ), creatinine ( $0.9 \pm 0.03$  mg/dl vs.  $1.0 \pm 0.03$  mg/dl,  $p = 0.17$ ) and body mass index ( $27.8 \pm 0.5$  kg/m<sup>2</sup> vs.  $29.7 \pm 0.9$  kg/m<sup>2</sup>,  $p = 0.39$ ) did not statistically differ between the two groups. Of 71 diabetic patients, 3 patients had type 1, 51 had type 2 diabetes, and for 17 diabetes patients the type was not specified. The mean values of HbA1c and blood sugar level were  $6.5 \pm 0.7\%$  and  $130.2 \pm 47.3$  mg/dl, respectively. The information with respect to diabetic medications was available for 46 diabetic patients. Of those, 2 patients had only lifestyle modification documented in their records. Seven patients were on insulin

therapy, and 1, 2, and  $\geq 3$  oral diabetic medications were taken in 20, 13 and 4 patients, respectively.

Overall, plaque was assessed in 3586 coronary artery segments in 142 patients. The measured CT variables including measured total segment numbers, length, vessel, lumen and plaque volumes at baseline and follow-up among non-diabetes and diabetes patients are listed in Table 2. The number of segments and lengths were higher in the non-diabetes group than in the diabetes group at both baseline and follow-up. At baseline, vessel volume, lumen volume and both absolute and normalized TPV and per-type plaque volumes did not differ between non-diabetes and diabetes patients. These trends were consistent in follow-up analyses except for the fibrous-fatty and LAP volumes which were higher in the group of diabetes patients.

Changes in each plaque volume between baseline and follow-up are summarized in Table 3. Compared to the non-diabetes group, absolute plaque volume changes in total plaque, non-calcified plaque, fibrous-fatty, and LAP were significantly greater in the diabetes group ( $p < 0.05$  for all) and a trend of fibrous volume changes toward significance was observed ( $p = 0.057$ ). The change in absolute calcified plaque volume was comparable between the two groups. When the change in normalized plaque volume was analyzed, total plaque, non-calcified plaque, fibrous-fatty, LAP volumes were significantly higher in the diabetes group compared to the non-diabetes group ( $p < 0.05$  for all). Normalized calcified plaque change was comparable between non-diabetes and diabetes patients.

Table 4 shows two models of multivariable linear regression analyses to predict normalized plaque volume progression after adjustment for age, gender, hypertension, dyslipidemia, current smoking and family history of CAD, history of PCI, aspirin use, statin use and the interval between the baseline and follow-up scans. Diabetes was significantly associated with progression of all types of plaque, i.e. total, non-calcified, fibrous, fibrous-fatty and LAP, but not calcified plaque. Baseline logCAC was also a predictor of plaque progression in total, non-calcified, fibrous and calcified plaque, whereas logCAC did not predict fibrous-fatty and LAP progression (Model 1). When baseline normalized non-calcified plaque volume instead of logCAC was included in the model, diabetes was similarly associated with plaque progression in all types of plaque, but not calcified plaque. The baseline normalized non-calcified plaque volume was also associated with total, non-calcified, fibrous, LAP and calcified plaque progression, also a trend towards progression in fibrous-fatty plaque was observed (Model 2).

**Table 1**  
Baseline characteristics among matched non-diabetes and diabetes patients.

	Non-diabetes (n = 71)	Diabetes (n = 71)	p value
<b>Baseline</b>			
Age (years) <sup>a</sup>	62.3 (57.0, 69.6)	66.9 (57.0, 73.0)	0.12
Male gender (%)	50 (70.4)	53 (74.6)	0.57
Hypertension (%)	41 (57.7)	46 (64.8)	0.39
Dyslipidemia (%)	43 (60.6)	44 (62.0)	0.86
Current smoking (%)	9 (12.7)	9 (12.7)	1.00
Family history (%)	40 (56.3)	43 (60.6)	0.61
History of percutaneous coronary intervention (%)	10 (14.1)	10 (14.1)	1.00
Interval years between baseline and follow-up scans <sup>a</sup>	3.1 (1.9, 4.6)	3.3 (2.0, 4.8)	0.57
CAC score <sup>a</sup>	351 (61, 1053)	275 (31, 1019)	0.81
CAC, n (%)			
0	9 (12.7)	5 (7.0)	0.65
1–99	13 (18.3)	19 (26.8)	
100–399	15 (21.1)	16 (22.5)	
400–999	15 (21.1)	13 (18.3)	
$\geq 1000$	19 (26.8)	18 (25.4)	

CAC, coronary artery calcium.

<sup>a</sup> Data are presented as median (interquartile range).

**Table 2**  
CT parameters of segment numbers, length, vessel, lumen and PVs at baseline and follow-up.

	Baseline			Follow-up		
	Non-diabetes (n = 71)	Diabetes (n = 71)	p value	Non-diabetes (n = 71)	Diabetes (n = 71)	p value
Segment numbers <sup>a</sup>	13 (12, 15)	13 (10, 14)	0.005	13 (12, 15)	13 (10, 14)	0.005
Length (mm)	481.5 ± 117.6	425.4 ± 123.5	0.006	481.4 ± 117.6	425.3 ± 123.3	0.006
Vessel volume (mm <sup>3</sup> )	3419.2 ± 1359.0	3113.2 ± 1177.5	0.15	3476.6 ± 1515.6	3173.0 ± 1247.8	0.20
Lumen volume (mm <sup>3</sup> )	2960.8 ± 1173.4	2698.8 ± 1109.2	0.17	2915.4 ± 1309.7	2602.2 ± 1146.0	0.13
<b>Absolute PV (mm<sup>3</sup>)</b>						
Total <sup>a</sup>	261.4 (66.8, 653.9)	306.5 (64.3, 655.6)	0.89	333.7 (140.5, 824.6)	477.3 (172.7, 856.6)	0.35
Non-calcified <sup>a</sup>	170.8 (27.7, 327.1)	178.1 (43.1, 419.5)	0.69	179.4 (67.6, 392.7)	284.3 (108.8, 516.8)	0.18
Fibrous <sup>a</sup>	137.6 (23.7, 297.5)	138.5 (36.5, 322.2)	0.85	158.3 (61.4, 371.1)	201.6 (88.0, 402.6)	0.35
Fibrous-fatty <sup>a</sup>	14.2 (0.9, 50.3)	25.8 (4.9, 61.6)	0.16	14.4 (4.9, 50.9)	41.3 (9.4, 96.7)	0.02
Low attenuation <sup>a</sup>	2.1 (0.0, 13.8)	5.1 (1.3, 15.4)	0.17	2.5 (0.5, 10.4)	9.6 (1.5, 34.1)	0.005
Calcified <sup>a</sup>	126.0 (15.6, 318.4)	79.0 (11.9, 247.9)	0.52	154.3 (30.7, 392.8)	128.3 (36.6, 339.3)	0.53
<b>Normalized PV (mm<sup>3</sup>)</b>						
Total <sup>a</sup>	202.8 (63.4, 576.1)	323.6 (61.6, 729.8)	0.43	294.4 (122.3, 809.3)	490.7 (195.0, 976.6)	0.10
Non-calcified <sup>a</sup>	158.8 (27.2, 307.6)	185.7 (37.5, 464.9)	0.26	190.4 (67.7, 377.6)	301.9 (101.3, 627.7)	0.03
Fibrous <sup>a</sup>	122.5 (24.1, 255.2)	146.3 (29.6, 339.3)	0.33	155.5 (62.5, 324.1)	236.1 (85.2, 487.5)	0.08
Fibrous-fatty <sup>a</sup>	13.0 (1.2, 45.9)	25.3 (5.6, 80.8)	0.06	13.2 (4.5, 45.5)	40.3 (10.8, 109.9)	0.003
Low attenuation <sup>a</sup>	2.0 (0.0, 13.3)	4.9 (1.3, 19.0)	0.07	2.4 (0.6, 9.8)	9.5 (2.1, 35.6)	0.001
Calcified <sup>a</sup>	105.9 (16.8, 294.4)	91.9 (11.0, 252.7)	0.85	170.2 (27.3, 382.2)	152.2 (36.1, 363.1)	0.93

PV, plaque volume.

<sup>a</sup> Data are presented as median (interquartile range).

**Table 3**  
Difference in PVs between baseline and follow-up among non-diabetes and diabetes patients.

	Non-diabetes (n = 71)	Diabetes (n = 71)	p value
<b>Absolute PV change (mm<sup>3</sup>)</b>			
Total <sup>a</sup>	53.4 (2.3, 158.6)	105.7 (16.0, 240.4)	0.03
Non-calcified <sup>a</sup>	28.9 (−0.1, 64.5)	53.7 (4.5, 148.4)	0.02
Fibrous <sup>a</sup>	27.5 (−0.1, 74.3)	40.0 (4.7, 119.9)	0.057
Fibrous-fatty <sup>a</sup>	0.7 (−5.8, 6.3)	4.5 (−1.3, 27.5)	0.02
Low attenuation <sup>a</sup>	0.1 (−2.3, 2.5)	2.4 (−0.6, 9.8)	0.002
Calcified <sup>a</sup>	19.9 (3.2, 99.2)	43.6 (0.8, 81.2)	0.78
<b>Normalized PV change (mm<sup>3</sup>)</b>			
Total <sup>a</sup>	52.8 (3.4, 133.7)	118.3 (28.6, 263.4)	0.005
Non-calcified <sup>a</sup>	26.4 (−0.2, 60.8)	52.3 (4.0, 166.7)	0.004
Fibrous <sup>a</sup>	25.5 (−0.2, 66.4)	41.6 (7.6, 134.2)	0.02
Fibrous-fatty <sup>a</sup>	0.8 (−5.3, 6.0)	4.3 (−1.1, 32.4)	0.01
Low attenuation <sup>a</sup>	0.1 (−2.3, 2.0)	3.0 (−0.7, 14.2)	0.001
Calcified <sup>a</sup>	26.5 (2.8, 88.4)	43.3 (0.8, 89.0)	0.43

PV, plaque volume.

<sup>a</sup> Data are presented by median (interquartile range).

**Table 4**  
Multivariable linear regression to predict normalized PV progression after adjustment for age, gender, hypertension, dyslipidemia, current smoking, family history, prior percutaneous coronary intervention, aspirin use, statin use, and interval years between baseline and follow-up scans.

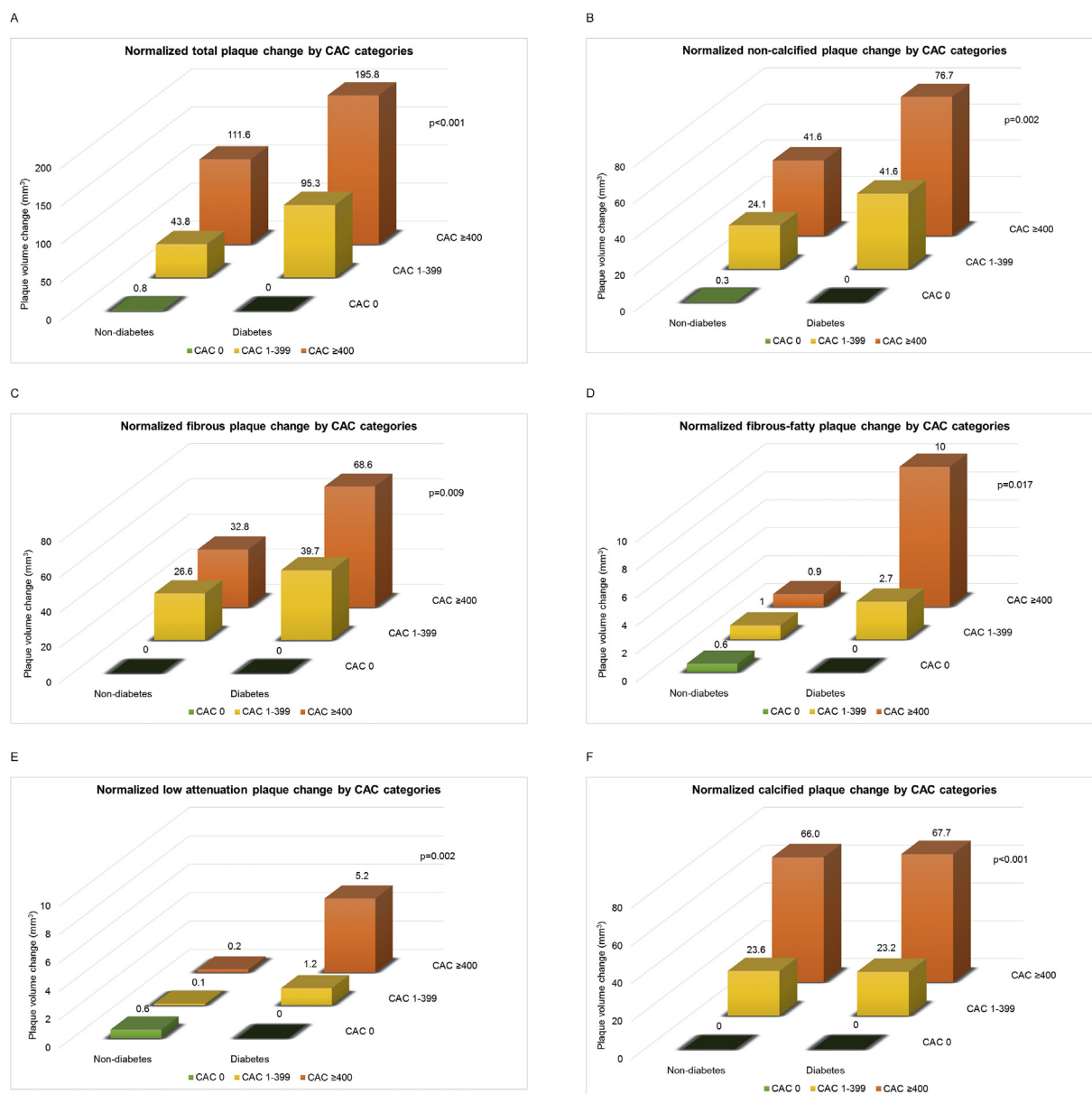
Model 1	β	95% CI	p value	Model 2	β	95% CI	p value
<b>Total</b>							
Diabetes	72.3	24.3120.3	0.003	Diabetes	50.7	2.8, 98.8	0.04
Baseline logCAC	26.0	14.7,37.2	<0.001	Baseline normalized non-calcified PV, mm <sup>3</sup>	0.2	0.1, 0.3	<0.0001
<b>Non-calcified</b>							
Diabetes	64.2	27.8100.7	<0.001	Diabetes	54.8	18.4, 91.1	0.003
Baseline logCAC	11.2	2.7,19.8	0.01	Baseline normalized non-calcified PV, mm <sup>3</sup>	0.09	0.02, 0.2	0.007
<b>Fibrous</b>							
Diabetes	34.7	7.4,62.0	0.01	Diabetes	28.4	0.9, 55.8	0.04
Baseline logCAC	8.3	1.9,14.7	0.01	Baseline normalized non-calcified PV, mm <sup>3</sup>	0.05	0.0, 0.1	0.03
<b>Fibrous-fatty</b>							
Diabetes	15.3	5.9,24.8	0.001	Diabetes	13.6	4.20, 23.1	0.005
Baseline logCAC	2.0	−0.3,4.2	0.09	Baseline normalized non-calcified PV, mm <sup>3</sup>	0.02	−0.0, 0.0	0.055
<b>Low attenuation</b>							
Diabetes	14.2	7.5,20.8	<0.001	Diabetes	12.8	6.3, 19.2	0.0001
Baseline logCAC	1.0	−0.5,2.6	0.19	Baseline normalized non-calcified PV, mm <sup>3</sup>	0.02	0.01, 0.03	0.002
<b>Calcified</b>							
Diabetes	3.8	−27.0,34.7	0.81	Diabetes	−7.8	−38.6, 23.0	0.62
Baseline logCAC	13.9	6.6,21.1	<0.001	Baseline normalized non-calcified PV, mm <sup>3</sup>	0.11	0.05, 0.2	0.0001

PV, plaque volume.

Fig. 1 illustrates changes in normalized plaque volumes between non-diabetes and diabetes patients by CAC categories with CAC 0, 1–399 and ≥ 400. Patients with higher CAC demonstrated greater volume changes in total, non-calcified, fibrous and calcified plaques in both the non-diabetes and diabetes groups (Fig. 1A–C and F). A linear relationship of fibrous-fatty and LAP progression within CAC categories was observed among diabetes patients; however, these changes were small and identical across a spectrum of the CAC groups among non-diabetes patients (Fig. 1D and E).

#### 4. Discussion

This is a first study providing in-depth evaluation of the association between diabetes and coronary atherosclerosis progression non-invasively detected by CCTA. We assessed the types of coronary plaque, i.e. total, non-calcified, fibrous, fibrous-fatty and LAP, and demonstrated that their plaque change over time was substantially positively higher in patients with diabetes compared to



**Fig. 1.** Normalized plaque volume change between diabetes and non-diabetes patients by coronary artery calcium score categories with 0, 1–399 and  $\geq 400$ . (A) total plaque volume, (B) non-calcified plaque volume, (C) fibrous plaque volume, (D) fibrous-fatty plaque volume, (E) low attenuation plaque, and (F) calcified plaque volume.

non-diabetic patients, whereas there were no differences in calcified plaque progression between the two groups. In addition, patients with higher CAC scores experienced progressive plaque volume increase over time in total, non-calcified, fibrous and calcified plaque, but the trend for increase in fibrous-fatty and LAPs was only observed among diabetes patients. In multivariable analyses, non-calcified plaque volume at baseline was also associated with plaque progression in total, calcified and non-calcified plaque, including LAP.

Clinical evidence of the association between diabetes and the progression in coronary atherosclerosis was also described by others. Raggi et al. found that, in diabetic patients, CAC progression was 17.7–33% greater compared to non-diabetic patients [25]. Similarly, our group has demonstrated that annual CAC progression in the diabetes group was approximately 3-fold greater than in the non-diabetes group [26]. In the IVUS study of 2237 subjects, diabetes patients showed a greater progression in percent atheroma

volume than non-diabetes patients ( $0.6 \pm 0.4\%$  vs.  $0.05 \pm 0.3\%$ ,  $p = 0.0001$ ) [27]. Although, these studies demonstrated that diabetes was associated with the progression of coronary atherosclerosis with regards to CAC score or partial plaque volume by IVUS, these studies did not provide in-depth evaluation of progression in coronary plaque components.

Coronary plaque characteristics, in particular non-calcified plaques are, in part, considered as one of important risk markers associated with future CVD events [17,28]. In previous autopsy studies, an extensive prevalence of necrotic core and inflammatory cells in coronary plaques was evident among diabetes subjects [29,30]. These findings may directly link to the increased risk in death [29,30], since these plaque features have been found as being at risk in plaque rupture associated with acute coronary syndrome and generally visualized as a part of non-calcified plaque on CCTA, especially LAP. Limited prior investigations have demonstrated the association between diabetes and plaque morphology and/or its

progression. Kristensen et al. have explored that diabetes patients were more likely to possess larger non-calcified plaque volume on CCTA and an increase in its volume was associated with future cardiac events [28]. In a study of 90 patients undergoing IVUS, Inaba et al. have found that increase in total lipid plaque volume was commonly observed among diabetes patients, but not in non-diabetes patients [31]. Our findings are similar with these studies, whereas these studies lack more detailed information with regards to non-calcified plaque components such as fibrous, fibrous-fatty and LAP. Our results supplement these studies as we have demonstrated that all the non-calcified components were progressively increased in diabetes patients compared to non-diabetes patients. Moreover, in the study by Inaba et al., diabetes patients possessed greater TPVs at baseline than non-diabetes patients. Diabetes is likely to be associated with greater overall plaque burden [14,32–35], in particular, non-calcified plaque volumes [36]. The presence of higher plaque burden may affect rapid atherosclerosis development since the presence of CAD by itself facilitates plaque progression [37–40]. For solving this major issue, we matched the baseline CAC other than clinical risk factors using a propensity-matching method between non-diabetes and diabetes patients to capture the pure effect of diabetes on plaque progression against a potential risk of global atherosclerotic burden. Indeed, we identified that increase in baseline CAC is also associated with greater plaque progression, especially in total, non-calcified, fibrous and calcified plaque regardless of diabetes.

One important finding of the current study is that larger non-calcified plaque volumes at baseline were associated with progression in LAP volumes. The finding may partially support the concept why larger non-calcified plaque volumes were associated with future cardiac events in the aforementioned study [28]. In the intravenous ultrasound (IVUS) study examining the dynamic nature of coronary atherosclerosis, all non-calcified plaque components by IVUS such as pathological intimal thickening (PIT), virtual histology IVUS derived thin-capped fibroatheroma (VH-TCFA), thick-capped fibroatheroma (ThCFA) and fibrotic plaque could convert to other type of non-calcified components [41]. Also, PIT, VH-TCFA and ThCFA are likely to increase in volume overtime compared to more pathologically stable plaque such as fibrotic and fibro-calcified plaques. Therefore, the non-calcified plaque burden itself may be a risk factor for accelerated non-calcified plaque progression, especially LAP, which in turn may increase the risk of acute coronary syndrome in the future.

Patients with extensive plaque burden are at high risk and likely to benefit from intensive statin therapy for preventing plaque progression [42]. Our findings confirm the current consensus to treat diabetes patients by intensive medical therapy such as statins, as suggested by the current prevention guideline [3]. Stabilization of coronary plaque and/or inhibition of plaque progression among individuals with diabetes are ultimate goals for preventing CVD events and might be achievable by intensive treatment with optimal medical therapy [3,43]. Numerous studies have proven the efficacy of statins to reduce coronary plaque volume [44,45]. Nevertheless, no studies have been conducted yet to investigate the risk reduction associated with stabilization of plaque activity or reduction in coronary plaque volume. In the current study, diabetes was associated with more extensive non-calcified plaque progression, although treatment with statins was more often prescribed in patients with diabetes compared to the non-diabetic subgroup. Of importance, the finding was consistent after adjustment for statin use in multivariable analyses. CCTA may be a good modality to triage diabetes individuals who are at high risk of future CVD events due to the direct visualization of subclinical atherosclerosis including non-calcified plaque [14,16]. A recent prospective randomized trial in 900 asymptomatic diabetes individuals

demonstrated that CCTA reduced risk of major adverse cardiovascular events by 20% compared to standard diabetes care; however, this failed to achieve statistical significance (HR 0.80, 95% CI 0.49–1.32,  $p = 0.38$ ) [46].

We have to acknowledge limitations of the current study. This is a retrospective single-center study. Because CCTA scans were clinically indicated in the present study, the application of our findings to population-based cohorts remains unknown. Additionally, we matched patients with or without diabetes to assess whether diabetes is associated with plaque progression in patients with similar risk factor profile; however, we could not match by unknown factors that may also promote plaque development. We did not match statin use at baseline which could affect stabilization of plaque volume over time. Thus, the identical calcified plaque progression between non-diabetes and diabetes patients across a spectrum of CAC groups could be explained by the attenuated impact of diabetes as a higher prevalence of patients were on statin therapy in the diabetes group. Given the small sample size, the plaque progression between subjects with and without diabetes could not be assessed by stratifying by statin treatment. Also, age is a great confounding variable affecting plaque progression. In the current study, sub-analysis by age was not performed. We do not have full history regarding multiple aspects of diabetes such as diabetes onset, duration, diabetic chronic renal disease or other diabetes complications that might have contributed to understanding the results of the study.

In the current study, in a matched cohort undergoing CCTA, diabetes was associated with greater plaque progression, in particular non-calcified plaque progression, compared to patients without diabetes. Our results clearly indicate the need for further clinical studies on stabilization and inhibition of progression of plaques and their associations with cardiovascular disease risk in diabetic patients. Therefore, our data strongly support the concept of implementation of current guidelines. Strict adherence to medical preventive therapies, such as those with efficacious statins, in diabetic patients are advised.

### Conflict of interest

Dr. Matthew Budoff is a consultant for General Electric; the other authors have no conflict of interest. Pieter Kitslaar is an employee of Medis medical imaging systems and has a research appointment at the Leiden University Medical Center.

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