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Multimodality Imaging of Anatomy and Function in Coronary Artery Disease

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Chapter 19

Non-Invasive Assessment of Plaque Characteristics with Multi-Slice Computed Tomography Coronary Angiography in Symptomatic Diabetic Patients

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Abstract

Background

Cardiovascular events are high in patients with type 2 diabetes while their risk stratification is more difficult. The higher risk may be related to differences in coronary plaque burden and composition. The purpose of the study was to evaluate whether differences in the extent and composition of coronary plaques in patients with and without diabetes can be observed using MSCT.

Methods

MSCT was performed in 215 patients (86, 40% with type 2 diabetes). The number of diseased coronary segments was determined per patient; each diseased segment was classified as showing obstructive ($\geq 50\%$ luminal narrowing) disease or not. In addition, plaque type (non-calcified, mixed and calcified) was determined. Plaque characteristics were compared in patients with and without diabetes. Regression analysis was performed to assess correlation between plaque characteristics and diabetes.

Results

Patients with diabetes showed significantly more diseased coronary segments compared to non-diabetic patients (4.9 ± 3.5 vs. 3.9 ± 3.2 , $p=0.03$) with more non-obstructive (3.7 ± 3.0 vs. 2.7 ± 2.4 , $p=0.008$) plaques. Relatively more non-calcified (28% vs. 19%), calcified (49% vs. 43%) and less mixed (23% vs. 38%) plaques were observed in diabetes ($p < 0.0001$). Diabetes correlated with the number of diseased segments, non-obstructive, non-calcified and calcified plaques.

Conclusions

Differences in coronary plaque characteristics on MSCT were observed between patients with and without diabetes. Diabetes was associated with higher coronary plaque burden. More non-calcified and calcified plaques while less mixed plaques were observed in diabetic patients. Thus, MSCT may be used to identify differences in coronary plaque burden, which may be useful for risk stratification.

Introduction

At present, 200 million people have diabetes mellitus worldwide while its prevalence is expected to continue increasing exponentially ¹. A close relationship between type 2 diabetes and the development of coronary artery disease (CAD) exists and cardiovascular disease is the main cause of death in this patient population ².

Non-invasive testing, including myocardial perfusion scintigraphy and dobutamine stress-echocardiography, has been used to detect CAD in diabetic patients ^{3,4} and a clear association between abnormal test results and worse outcome has been demonstrated similar to the general population ⁶. Nonetheless, after normal findings, still elevated event rates are observed in diabetic patients as compared to non-diabetic individuals ^{6,7}, indicating a need for further refinement of prognostification in this population. The higher event rates in patients with diabetes as compared to patients without diabetes could be related to differences in coronary plaque burden and composition. Therefore, direct visualization of coronary plaque burden could be a useful tool for risk stratification. Indeed, using invasive techniques, a considerably higher extent of CAD and plaque burden has been demonstrated in the presence of diabetes ^{8,9}.

To date, atherosclerosis has been non-invasively assessed in patients with type 2 diabetes using coronary calcium scoring revealing extensive atherosclerosis ^{5,6}. Still, coronary calcium scoring may seriously underestimate coronary plaque burden as non-calcified lesions are not recognized ⁷. More recently, contrast-enhanced multi-slice computed tomography (MSCT) coronary angiography has become available which allows, in contrast to calcium scoring, detection of both calcified and non-calcified coronary lesions ⁸⁻¹¹. As a result, the technique potentially allows a more precise non-invasive evaluation of coronary atherosclerosis, which in turn could be valuable for improving risk stratification. Accordingly, the purpose of the present study was to evaluate whether differences in the extent and composition of coronary plaques in patients with diabetes as compared to patients without diabetes can be observed with MSCT.

Methods

The study population consisted of 86 (40%) patients with known type 2 diabetes mellitus and 129 (60%) patients without diabetes mellitus who underwent examination with MSCT coronary angiography for recurrent chest pain complaints. Fifty-one (24%) patients were examined with 16-slice MSCT scanner, while the majority (164, 76%) underwent examination with 64-slice MSCT. Diabetes was diagnosed according to the criteria set by American Diabetes Association ¹²: 1) symptoms of diabetes and casual plasma glucose level of ≥ 11.1 mmol/l or 2) fasting plasma glucose level of ≥ 7.0 mmol/l. Only patients in sinus rhythm, without contraindications to MSCT were included ¹³. All patients gave written informed consent to the study protocol, which was approved by local ethics committee.

MSCT data acquisition

All examinations were performed using Toshiba Multi-slice Aquilion systems (Toshiba Medical Systems, Tokyo, Japan). First, a prospective coronary calcium scan without contrast enhancement was performed, followed by 16- or 64-slice MSCT coronary angiography performed according to the protocols described elsewhere^{14,15}. If the heart rate was ≥ 65 beats/min additional oral β -blockers (metoprolol, 50 or 100 mg, single dose, 1 hour prior to the examination) were provided if tolerated.

MSCT data analysis

Coronary artery calcium score

Coronary artery calcium was identified as a dense area in the coronary artery exceeding the threshold of 130 HU. Total Agatston score was recorded for each patient.

Coronary plaque assessment

MSCT angiograms were evaluated by two experienced observers who were unaware of the clinical history of the patients. Coronary arteries were divided into 17 segments according to the modified American Heart Association classification¹⁶. The presence of coronary plaques was visually evaluated using axial images and curved multiplanar reconstructions. One coronary plaque was assigned per coronary segment. Plaques were classified as obstructive and non-obstructive using a 50% threshold of luminal narrowing. As shown in Figure 1, three types of plaques were identified: 1. non-calcified plaques=plaques having lower density compared with the contrast-enhanced vessel lumen, 2. calcified plaques=plaques with high density and 3. mixed plaques=plaques with non-calcified and calcified elements within a single plaque. The presence of coronary plaques on MSCT, the presence of obstructive CAD in general and if located in left main (LM)/left anterior descending (LAD) coronary artery as well as the presence of obstructive CAD in one vessel (single vessel disease) or two or three vessels (multi-vessel disease) were evaluated. For each patient, the number of diseased coronary segments (segments containing plaques or previously implanted stents), the number of coronary segments with non-obstructive as well as obstructive plaques were determined. Also, the number of segments with respectively non-calcified, mixed and calcified plaques was determined.

Statistical analysis

Categorical variables were expressed as numbers (percentages) and compared between groups with Chi-square test. Continuous variables were expressed as mean (standard deviation) and compared with the two-tailed t-test for independent samples. When not normally distributed, continuous variables were expressed as medians (interquartile range) and compared using nonparametric Mann-Whitney test.

To determine the relationship between plaque characteristics and the presence of diabetes linear regression analysis was performed when dependent variable was continuous and logistic regression

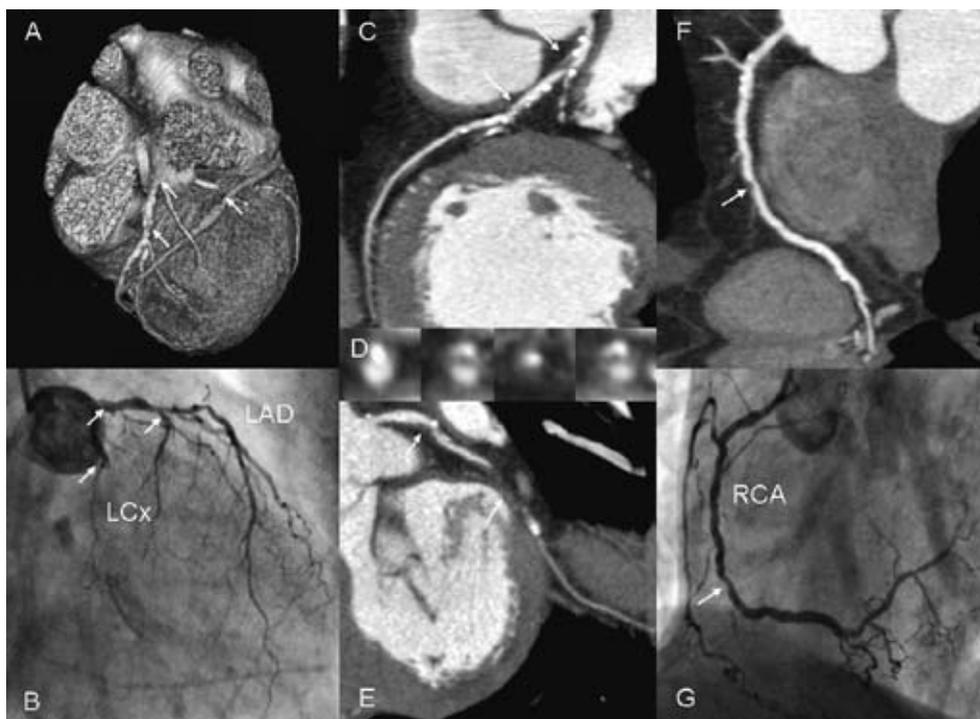


Figure 1. An example of diffuse atherosclerosis demonstrated on MSCT coronary angiography in a patient with type 2 diabetes. Three-dimensional volume rendered reconstruction depicts severe narrowing of the proximal and mid- left anterior descending coronary artery (LAD) and occluded left circumflex coronary artery (LCx) (A). The findings were confirmed by conventional coronary angiography (B). Curved multiplanar reconstruction and the corresponding transversal sections of the LAD show multiple obstructive mixed plaques in the whole course of the artery (C, D). A non-obstructive plaque followed by vessel occlusion was demonstrated in the LCx coronary artery (E). Diffuse non-obstructive calcified plaque and an obstructive non-calcified plaque were seen in the right coronary artery (RCA) (F), which was confirmed by conventional coronary angiography (G).

analysis was performed when dependent variable was categorical. First univariate analysis was performed, followed by multivariate analysis with correction for the following variables: age, gender, risk factors for CAD, clinical presentation (typical angina pectoris or atypical chest pain together with the presence of multiple CAD risk factors) and use of statins.

P-values <0.05 were considered as statistically significant. Statistical analyses were performed using SPSS software (version 12.0, SPSS Inc, Chicago, IL, USA) and SAS software (The SAS system, release 6.12, Cary, NC, USA: SAS Institute Inc.).

Results

Baseline characteristics of patients with diabetes and without diabetes are provided in Table 1. In total, 215 patients (136, 63% men, mean age 58 ± 11 years) were included of which 86 (40%) were patients with known type 2 diabetes mellitus. Ninety-six (45%) patients used statins (41 (48%)

Table 1. Characteristics of patients with diabetes and without diabetes.

	All patients (n=215)	Patients with diabetes (n=86)	Patients without diabetes (n=129)
Age (yrs)*	58±11	56±11	59±12
Male gender	136 (63%)	56 (65%)	80 (62%)
Hypercholesterolemia	114 (53%)	53 (62%)	61 (47%)
Arterial hypertension	107 (50%)	48 (56%)	59 (46%)
Smoking	80 (37%)	33 (38%)	47 (36%)
Family history of CAD	82 (38%)	30 (35%)	52 (40%)
Body mass index (kg/m ²)*	27±4	28±5	26±4
Obesity	37 (17%)	20 (24%)	17 (14%)
Cardiac history			
Previous MI*	41 (19%)	8 (9%)	33 (26%)
Previous PCI*	42 (20%)	9 (11%)	33 (26%)

* $p < 0.05$ between patients with and without diabetes.

Data are mean±SD or n (%).

CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

patients with diabetes, 55 (43%) without diabetes, $p=0.47$), 91 (42%) aspirin, 78 (36%) β -blockers and 69 (32%) angiotensin converting enzyme inhibitors. Patients with diabetes mellitus were significantly younger as compared to patients without diabetes, had a higher mean body mass index and lower prevalence of previous CAD.

MSCT plaque characteristics

Total patient population

Coronary plaque characteristics on MSCT in the entire population and in patients presenting with or without diabetes mellitus are presented in Table 2 and Figure 2. After exclusion of 64 (2%) segments with non-diagnostic quality ($n=11$ small caliber, $n=45$ motion artefacts due to elevated heart rate, $n=8$ increased signal-to-noise ratio), a total of 2941 coronary segments were included in the analysis. CAD was completely absent on MSCT in 41 (19%) patients. In the remaining 174 (81%) patients 917 (31%) segments with plaques ($n=871$, 29%) or previously implanted stents ($n=46$, 2%) were observed. Of segments containing plaques, 675 (77%) showed non-obstructive and 196 (23%) showed obstructive CAD. In general, non-calcified plaques were observed in 204 (23%) segments, mixed in 271 (31%) and calcified in 396 (46%).

Diabetic patients versus non-diabetic patients

As can be derived from Table 2, the average number of diseased segments was higher in patients with diabetes (4.9 ± 3.5) as compared to non-diabetic patients (3.9 ± 3.2), $p=0.03$. Particularly non-obstructive coronary plaques were more frequently observed on MSCT in the former population (Figure 2 A). In addition, CAD tended to be more severe in diabetic patients as both LM/LAD disease and multi-vessel

Table 2. MSCT plaque characteristics in the whole study population and comparison between patients with diabetes and without diabetes.

	All patients (n=215)	Patients with diabetes (n=86)	Patients without diabetes (n=129)
Patients			
Coronary plaques on MSCT	174 (81%)	73 (85%)	101 (78%)
Obstructive CAD	80 (37%)	34 (40%)	46 (36%)
Single vessel disease	43 (20%)	16 (19%)	27 (21%)
Multi-vessel disease	37 (17%)	18 (21%)	19 (15%)
Obstructive CAD in LM/LAD	61 (28%)	29 (34%)	32 (25%)
Total Agatston calcium score	73 (0-387)	72 (0-372)	74 (0-391)
Segments			
Nr of diseased segments*	4.3±3.4	4.9±3.5	3.9±3.2
Nr of segments with obstructive plaques	0.9±1.7	1.0±1.8	0.9±1.6
Nr of segments with non-obstructive plaques*	3.1±2.7	3.7±3.0	2.7±2.4
Nr of segments with non-calcified plaques*	1.0±1.6	1.3±2.0	0.7±1.2
Nr of segments with mixed plaques	1.3±1.8	1.1±1.5	1.4±2.0
Nr of segments with calcified plaques*	1.8±2.4	2.3±2.8	1.5±2.1

* $p < 0.05$ between patients with and without diabetes.

Data are mean±SD, median (interquartile range) or n (%).

CAD, coronary artery disease; LAD, left anterior descending coronary artery; LM, left main coronary artery; MSCT, multi-slice computed tomography.

disease were more frequently diagnosed, although the difference did not reach statistical significance. Concerning plaque types however, significant differences were observed in between diabetic and non-diabetic patients since patients with diabetes presented with significantly more segments containing non-calcified plaques (1.3 ± 2.0 versus 0.7 ± 1.2 , $p = 0.005$) as well as calcified plaques (2.3 ± 2.8 versus 1.5 ± 2.1 , $p = 0.02$). Accordingly, also the relative distribution of plaque types, which is illustrated in Figure 2 B, differed since plaques in patients with diabetes were more frequently either non-calcified (114/406, 28% versus 90/465, 19%) or calcified (198/406, 49% versus 198/465, 43%). In contrast, plaques in patients with diabetes were less frequently mixed (94/406, 23% versus 177/465, 38%), $p < 0.0001$.

Correlation of MSCT plaque characteristics and diabetes

The results of uni- and multivariate analyses of the correlation between MSCT plaque characteristics and the presence of diabetes are depicted in Table 3. After correction for baseline characteristics, the correlation of the number of diseased coronary segments as well as the number of segments with non-obstructive plaques and the presence of diabetes remained statistically significant. Concerning plaque type, both the number of coronary segments with non-calcified and calcified plaques remained significantly correlated with diabetes.

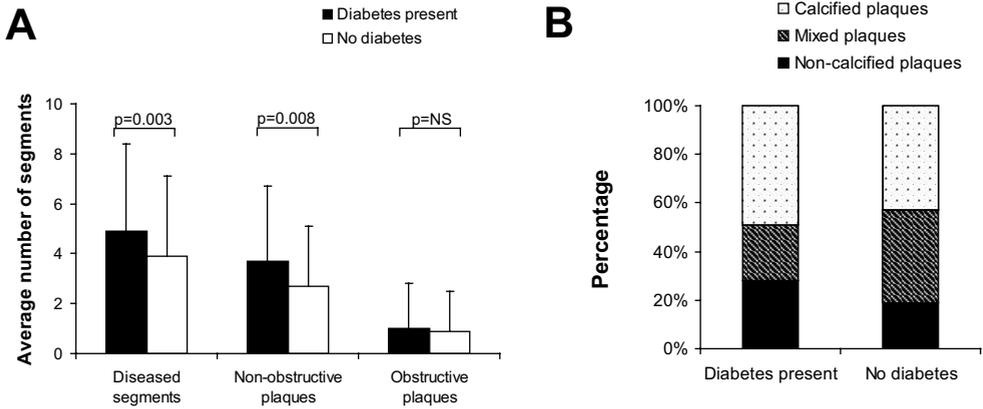


Figure 2. A. Clustered columns demonstrating the distribution of diseased coronary segments, segments with non-obstructive and obstructive plaques in diabetic and non-diabetic patients. B. Bar graph demonstrating the relative distribution of coronary segments with different plaque types in patients with diabetes mellitus and without diabetes ($p < 0.0001$).

Table 3. Estimates of correlation of MSCT plaque characteristics with the presence of diabetes.

MSCT characteristics	Univariate		Multivariate	
	Parameter estimate	p-value	Parameter estimate	p-value
Patients				
Total Agatston calcium score	127.91	0.11	139	0.08
Coronary plaques on MSCT	1.56 (0.76-3.21)	0.23	1.35 (0.56-3.26)	0.50
Non-obstructive CAD	1.53 (0.70-3.32)	0.28	1.11 (0.42-2.94)	0.83
Obstructive CAD	1.59 (0.72-3.52)	0.25	2.09 (0.68-6.49)	0.20
Obstructive CAD in LM/LAD	1.70 (0.77-3.74)	0.19	2.89 (0.90-9.31)	0.08
Single vessel disease	1.11 (0.46-2.67)	0.82	1.35 (0.43-4.29)	0.61
Multi-vessel disease	1.77 (0.72-4.35)	0.21	4.78 (0.66-34.37)	0.12
Segments				
Nr of diseased segments	1.01	0.03	1.51	0.0004
Nr of segments with obstructive plaques	0.13	0.58	0.33	0.17
Nr of segments with non-obstructive plaques	0.99	0.008	1.27	0.0005
Nr of segments with non-calcified plaques	0.63	0.006	0.69	0.004
Nr of segments with mixed plaques	-0.28	0.28	0.03	0.91
Nr of segments with calcified plaques	0.77	0.02	0.88	0.008

Data are odds ratios (CI) or estimates of correlation.

CAD, coronary artery disease; LAD, left anterior descending coronary artery; LM, left main coronary artery; MSCT, multi-slice computed tomography.

Discussion

In the present study, differences in coronary plaque characteristics between patients with and without diabetes mellitus were observed using MSCT coronary angiography. A significant, positive correlation between the presence of diabetes and coronary plaque extent was demonstrated. In particular, diabetes was associated with an increased number of non-obstructive plaques, indicating more diffuse CAD as compared to patients without diabetes. Also, differences in the distribution of coronary plaque types were observed, with diabetic patients showing more non-calcified and calcified plaques and less mixed plaques.

Plaque burden

In the present study, a larger plaque burden was observed in patients with diabetes. Similar observations have been reported in previous invasive as well as postmortem studies^{5,17,18}. Nicholls et al recently reported observations in 654 subjects (including 128 with diabetes) using intravascular ultrasound; the authors demonstrated that diabetes was a strong, independent predictor of percent plaque volume and total atheroma volume, indicating that diabetes appears to be associated with a substantial increase in (diffuse) plaque burden¹⁸.

In addition, diabetes was associated with more non-obstructive plaques in current study. This has also been observed in studies using invasive coronary angiography^{8,9}. The increased total plaque burden may be related with the increased event rate, as observed in diabetic patients. Moreover, it has been suggested that plaque rupture may occur often in non-obstructive lesions, referred to as vulnerable plaques²⁴⁻²⁷. Many of these non-obstructive lesions will not be associated with stress-inducible ischemia, resulting in normal results on functional imaging tests, such as nuclear imaging or stress echocardiography^{28,29}. Whether the larger total plaque burden and the increased prevalence of non-obstructive lesions in diabetic patients translate into a higher event rate remains to be determined in future studies.

Plaque composition

Another important finding of the present study is the difference in distribution of different coronary plaque types between patients with and without diabetes. Relatively more non-calcified and calcified plaques were observed in patients with diabetes. At the same time, the proportion of mixed plaques (possibly regarded as an intermediate phase of coronary plaque development) was significantly lower in patients with diabetes. Accordingly, these observations could suggest a more rapid development of atherosclerosis in the presence of diabetes, with faster progression from non-calcified lesions to completely calcified lesions. A faster progression of atherosclerosis in patients with diabetes has been suggested previously based on event rates in patients undergoing nuclear perfusion imaging^{19,20}. In the general population, a normal perfusion scan is associated with a low (<1%) hard event rate which is sustained over long-term follow-up. In patients with diabetes, the hard event rate is equally low in the first 2 years in patients with a normal perfusion scan, but an increased event rate (despite the

initial normal myocardial perfusion scan) is observed after 2 years follow-up. This observation has been considered to be related to a faster progression of CAD in diabetic patients.

The increased prevalence of both non-calcified and calcified plaques may also have implications for calcium scoring. In a recent study by Raggi et al, 10,377 asymptomatic individuals (including 903 patients with diabetes) were followed for a period of 5 ± 3.5 years after coronary calcium scoring with electron beam computed tomography³¹. Higher mortality was observed in diabetic patients as compared to non-diabetic patients despite similar coronary calcium scores, a finding which was observed for every level of coronary calcification. The authors hypothesized that the difference in prognosis in diabetic and non-diabetic patients despite similar calcium load could be attributed to the presence of extensive diffuse non-calcified atherosclerosis, which could not be detected by calcium scoring. In line with these suggestions, the current study indeed demonstrated the presence of diffuse atherosclerosis with a significantly higher amount of non-calcified coronary plaques in the diabetic patients. Accordingly, calcium scores may underestimate total coronary plaque burden to higher extent in patients with diabetes, and thus, MSCT coronary angiography may have substantial incremental value over coronary calcium scoring, although this concept needs further study.

Limitations

This study is a comparative study, describing coronary atherosclerosis in patients with and without diabetes. Examinations were performed at a single time point and were not repeated over time. Also, MSCT angiograms were evaluated visually since no reliable quantitative algorithms are currently available. Two scanner generations (16- and 64-slice MSCT) were used during the study, which could have affected the accuracy of detection of different plaque types. Follow-up data are not yet available and these data are needed to determine whether the observations on MSCT may provide prognostic information and may potentially be used to identify diabetic patients at increased risk. Finally, patients in the present study were referred for non-invasive cardiac evaluation of chest pain with known or suspected CAD. Accordingly, the findings may not be applicable to asymptomatic diabetic patients.

In addition, several limitations of MSCT in general should be mentioned. MSCT is still associated with an elevated radiation dose, while also the administration of contrast media is required. Finally, the presence of ischemia cannot be determined on MSCT and abnormal MSCT findings should ideally be combined with functional data.

Conclusions

Differences in coronary plaque characteristics on MSCT were observed between patients with diabetes and without diabetes. Diabetes may be associated with a higher coronary plaque burden as determined on MSCT. Also, more non-calcified and calcified plaques in combination with less mixed plaques were observed in patients with diabetes, possibly reflecting faster progression of CAD in the presence of diabetes. MSCT may be used to identify differences in coronary plaque burden, which may eventually be useful for risk stratification of patients with diabetes.

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