Endocrine Care
doi: 10.4183/aeb.2014.238

ASYMPTOMATIC CORONARY ARTERY DISEASE IN TYPE 2 DIABETES MELLITUS PATIENTS COMPARED TO A NON-DIABETIC CONTROL GROUP

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Abstract

Background. Coronary artery disease (CAD), often asymptomatic, is the most common cause of morbidity, mortality and costs in diabetes. Early detection of CAD in patients with diabetes may be of paramount importance and substantially improve the outcome in diabetic patients.

Objective. The aims of the current study were to determine if there are significant differences concerning the prevalence of occult CAD in asymptomatic type 2 diabetic patients compared to asymptomatic non-diabetic patients.

Design, subjects and methods. The authors retrospectively reviewed a group of 120 non-diabetic (77 men, 43 women, mean age 61±10.2 years) and 120 diabetic (81 men, 39 women, mean age 58±11.4 years) asymptomatic patients that underwent coronary computed tomography angiography (CCTA) for various reasons between January 2013 and January 2014.

Results. Coronary plaques were identified in 105 diabetic patients (87.5%) and in 75 non-diabetic patients (62.5%) the prevalence being significantly different (p=0.023). Regarding plaque composition and degree of stenosis, we found a higher prevalence of calcified (p=0.016) and significantly stenotic (≥50% luminal narrowing) plaques (p=0.008) in the diabetic group. Agatston calcium score, relevant for atherosclerotic plaque load, was higher (p=0.005) in type 2 diabetic patients (350.3) compared to non-diabetic patients (158.7).

Conclusion. CCTA could represent a screening method able to detect silent atherosclerotic plaques thus contributing to the prevention of acute coronary syndrome (ACS) by an early and adequate treatment of CAD. Obstructive atherosclerotic plaques can be accurately identified using CCTA, limiting the use of invasive imaging methods and selecting patients that could benefit of coronary revascularization.

Key words: coronary artery disease, type 2 diabetes mellitus, coronary computed tomography angiography, calcium score, coronary stenosis.

INTRODUCTION

Cardiovascular diseases (CVD) represent a major cause of morbidity and mortality in general population, identification of groups at high

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risk of myocardial ischemic events thus developing as a necessary strategy intended to reduce subjacent complications and deaths.

Diabetes Mellitus (DM) is a proatherogenic condition characterized by a high probability of coronary events caused by its development at the confluence of multiple pathogenic mechanisms. Neuropathy, a microvascular complication of DM, is frequently associated with asymptomatic macrovascular complications, such as coronary and peripheral artery disease. DM is a public health problem, more than 347 million persons worldwide being diagnosed with DM at the end of 2012, with a prediction of 552 million cases in 2030. In Romania, the prevalence of DM has increased from 7.6% in 2007 to 8.4% in 2010, and the incidence reported by the Health Ministry in 2010 was of 319.1 new cases for 100.000 inhabitants. World Health Organization (WHO) stated that direct costs of DM and related diseases represent up to 15% of the Health Ministries' budget. People suffering from type 1 and type 2 DM are at high risk for CVD, especially coronary artery disease (CAD), the leading cause of diabetes related morbidity and mortality; the 10-year mortality rate in diabetic patients with CAD exceeds 70% (1-4).

Multidetector Computed Tomography (MDCT) facilitates the noninvasive study of coronary arteries in patients with chest pain, various atherosclerotic symptoms, or multiple risk factors for CAD, through the determination of calcium deposits in the vascular tree (Agatston Calcium Score), detection and characterization of atherosclerotic plaques, and quantification of coronary stenoses.

The objectives of the current study were to determine if there are differences in the prevalence of occult CAD in asymptomatic type 2 diabetic patients compared to asymptomatic non-diabetic patients.

MATERIAL AND METHODS

Study design

The current study was designed as a retrospective case-control evaluation carried out in the Radiology Department of the Institute for Cardiovascular Diseases, Iasi, Romania. All patients underwent CCTA between January 2013 and January 2014. Informed consent prior to examination was obtained in all cases.

Study groups

The authors retrospectively reviewed a group of 120 non-diabetic and a group of 120 diabetic asymptomatic patients that underwent CCTA for various reasons, such as preoperative evaluation of coronary arteries in patients suffering from valvular or aortic diseases, screening for CAD in patients with risk factors, atrial fibrillation prior to radiofrequency ablation therapy. Patients presenting ACS or ECG alterations compatible with myocardial ischemia or necrosis (pathologic Q waves, ST segment depression of more than 1 mm, negative T waves, left bundle branch complete block), with prior evidence or under treatment for CAD (antecedents of stable or unstable angina pectoris, myocardial infarction, coronary revascularization),

were not included in the study.

DM was defined as fasting plasma minimal glucose level of more than 126 mg/dL (6.99 mmol/L) or 2–h plasma glucose ≥ 200mg/dL (11.1mmol/L) currently treated with dietary intervention, oral glucose-lowering agents, or insulin.

Image acquisition protocol

All 240 patients were examined using a 2nd generation 256-slices dual source MDCT scanner (Siemens Somatom Definition Flash, Siemens Medical Solutions, Germany) with the following scan parameters: 100 or 120 kV tube voltage, tube current modulated by CareDose 4D algorithm (320 mAs reference), 128 x 0.6 mm collimation, gantry rotation time 280 ms.

Depending on heart frequency and cardiac pathology there were used two imaging protocols:

a) High pitch retrospective scanning in patients with high (more than 71 beats per minute) or irregular heart rates in order to perform end-systolic phase reconstructions;

b) High pitch prospective scanning in patients with stable heart rate (less than 70 beats per minute).

In the morning of the examination it was administered orally 50 mg Metoprololum (Metroprolol LPH 50 mg, LaborMed Pharma S.A., Romania) to each patient in case of no contraindication present. Test bolus injection protocol was used in all cases for optimal contrast timing. A volume of 20 ml of contrast agent (Iomeron 400, Bracco, Milan, Italy) followed by 25 ml of saline chaser were injected via an 18G cannula placed in the right mediobasilic or mediocephalic vein at a flow rate of 6 ml/sec. A series of dynamic, low-dose monitoring scans were performed (region of interest in the ascending aorta) beginning 10 seconds after initiation of contrast agent injection in order to determine the time interval between the start of the test bolus injection and the peak of aortic enhancement. After the aortic peak time evaluation (APT) 2 puffs of nitroglycerin (0.8 mg) were administered sublingually for coronary artery dilation, thus allowing the start of the main examination. An average volume of 85 ml of contrast media and 50 ml of saline chaser were injected and scanning in a single breath hold began after a delay based on the previously determined APT+5 seconds. Optimal reconstructions at different R-R interval percentages were performed (thickness 0.75 mm). Images were reconstructed at 30-80% of the R-R interval in 5% increments while the optimal reconstruction interval was chosen for image analysis on a Syngo. via workstation (Siemens Medical Solutions, Germany) by two independent radiologists, in order to obtain more objective results.

Renal function was evaluated on the day of examination in all cases. In patients treated with metformin derivate, the medication was suspended 48 hours after the examination and reinitiated after a renal function control in order to avoid lactic acidosis. No special precautions were taken in case of patients treated with insulin.

Image analysis started with evaluation of the calcium score on the

non-contrast acquisition (3 mm thick axial images) using the incorporated Agatston score evaluation algorithm. The Agatston calcium score was classified in 5 categories, based on the cut-off points widely used in the literature:

- ≤ 10 - minimal or insignificant CAD;
- 11-100 – mild CAD;
- 101-400 – moderate CAD;
- 401-1000 – severe CAD;
- >1000 - very extensive, diffuse CAD.

Images obtained after contrast examination (0.75 mm thick) were analyzed using the syngo. CT Coronary Analysis software application. Coronary arteries were evaluated by two radiologists on axial images, curve plane reconstructions (CPR), multiplanar reformations (MPR), maximum intensity projections (MIP), volume rendering (VR). Atherosclerotic plaques were defined as structures that caused an intima-media thickening (IMT) of more than 1 mm within or adjacent to the vessel lumen. The following parameters were assessed: atherosclerotic plaque type (calcified, noncalcified, mixed, ulcerated or thrombotic), presence of coronary stenosis, degree of stenosis (less than 50%; equal or more than 50%), number of affected vessels (single or multi-vessel disease), location and number of stenoses. After conducting independent assessments, an interpretation of consensus was reached in order to ascertain a final diagnosis.

Statistical analysis

Statistical tests were performed using XLSTAT add-in for Excel 2011 (Mac OS X platform). Quantitative data was tested for normality and presented as mean value ± standard deviation (SD). Student's t test and analysis of variance (ANOVA) were used for comparisons of mean values between groups. Qualitative data was presented as percentages and compared using Chi-square of Fisher's exact test. A p value of less than 0.05 was considered significant.

RESULTS

Clinical characteristics of study groups

Clinical characteristics of patients included in the diabetic study group *versus* the nondiabetic study group are summarized in Table 1. In case of diabetic patients, average time from diagnosis of type 2 DM was of 90±51 months (range 6 – 204 months).

Table 1. Clinical characteristics of patients included in the study groups: T2DM group (n=120) and control non-diabetic group (n=120)

	Diabetic patients	Non-diabetic patients	p
Age (mean ± SD)	58±11.4 years	61±10.2 years	n.s.
Sex ratio (M/F)	81/39	77/43	n.s.
Body mass index (kg/m^2)	27.8±4.2	28.5±3.5	n.s.
Cardiovascular risk factors			
Arterial hypertension	86 (71.67%)	72 (60%)	0.02
Dyslipidemia	82 (68.33%)	71 (59.17%)	0.08
Current smoker	51 (42.5%)	55 (45.83%)	n.s.
Familial history	63 (52.5%)	58 (48.33%)	n.s.
Obesity	48 (40%)	29 (24.17%)	0.003

Twenty-eight patients (23.33%) were diagnosed with diabetic nephropathy, 22 (18.33%) with diabetic retinopathy, 30 patients (25%) with diabetic neuropathy, 8 patients (6.67%) with cerebrovascular disease, and 26 patients (21.67%) with peripheral artery disease.

No significant differences were found between the two groups concerning lipid profile and plasma creatinine. Microalbuminuria registered higher values in diabetic group due to the fact that 23.33% of these patients already had nephropathy (Table 2).

Coronary plaques were identified in 105 of the diabetic patients (87.5%) and in 75 of the non-diabetic patients (62.5%) the prevalence being significantly different (p=0.023), but the number of affected vessels registered similar percentages in the two groups (Table 3).

Most of coronary stenoses were located on the left anterior descending artery (LAD), both in diabetic (87.62%) and non-diabetic patients (92%), followed by the left circumflex (50% of diabetic patients and 56% of non-diabetic patients) and right coronary artery (52.38% of diabetic patients and 42.67% of non-diabetic patients) with no differences between the groups.

Agatston calcium score, a relevant variable for atherosclerotic plaque load, was significantly higher (p=0.005) in type 2 diabetic patients (350.3) compared to non-diabetic patients (158.7) (Table 4) (Fig. 1).

Table 2. Blood and urine test results comparison between the study groups: T2DM group (n=120) and control non-diabetic group (n=120)

	Diabetic patients	Non-diabetic patients	p
Total cholesterol (mg/dL)	210.1±50.2	205.3±43.2	n.s.
LDL cholesterol (mg/dL)	125.4±45.1	124.7±35.8	n.s.
HDL cholesterol (mg/dL)	46.3±12.2	50.6±19.7	n.s.
Triglycerides	158.2±75.4	163±94.8	n.s.
Plasma creatinine (mg/dL)	1.0±0.7	1.1±0.4	n.s.
Microalbuminuria (mg/dL)	105.3±95.2	43.7±37.8	0.002

Table 3. Number of affected vessels in diabetic *versus* non-diabetic patients

Number of affected vessels	Diabetic patients	Non-diabetic patients	p
1 affected vessel	33 (32.67%)	27 (36%)	
2 affected vessels	23 (21.90%)	14 (18.67%)	0.12
≥3 affected vessels	49 (46.67%)	33 (44%)	

Table 4. Agatston calcium score in type 2 diabetic patients (n=120) compared to non-diabetic patients (n=120)

Agatston score	Diabetic patients	Non-diabetic patients	p
Total	350.3±215.7	158.7±237.2	0.005
<10	11 cases (10.47%)	15 cases (20%)	
11-100	23 cases (21.90%)	32 cases (42.67%)	
101-400	35 cases (33.33%)	11 cases (14.67%)	0.004
401-1000	32 cases (30.48%)	15 cases (20%)	
>1000	4 cases (3.81%)	2 cases (2.67%)	

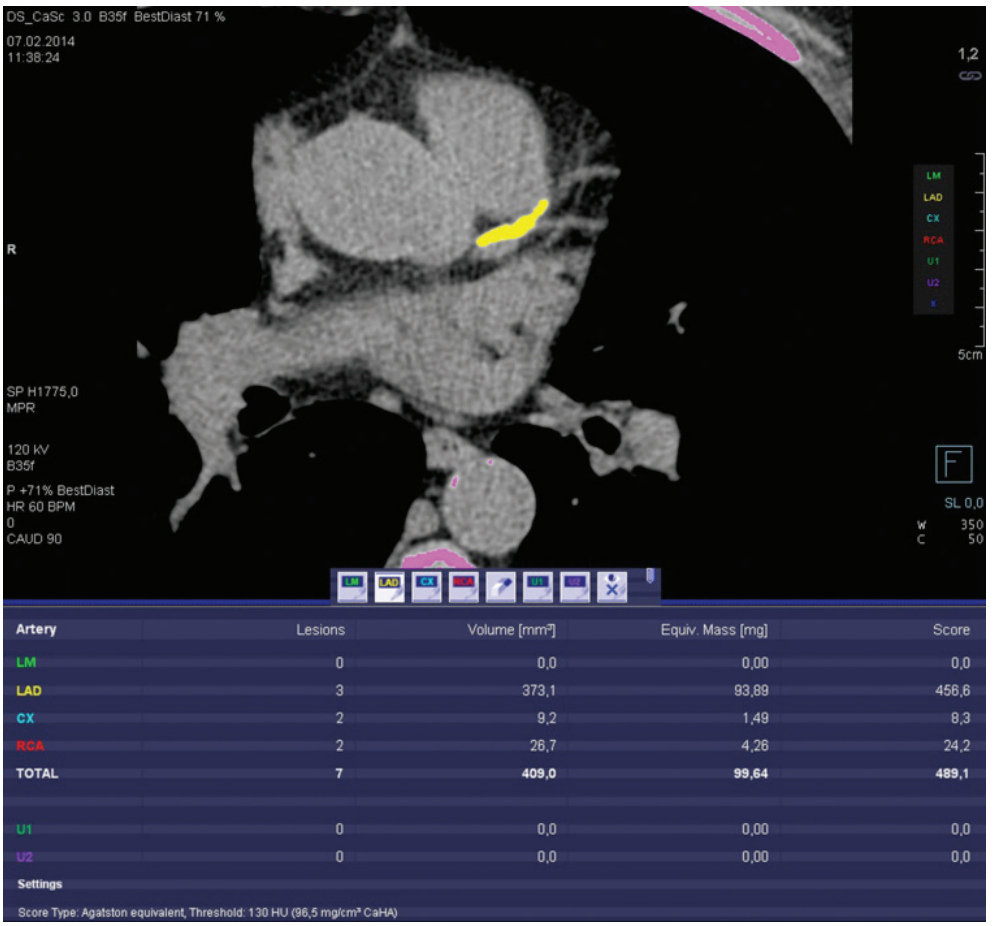

Figure 1. Calcium score evaluation in a diabetic patient.

Table 5. Atherosclerotic plaque composition in type 2 diabetic patients (n=120) compared to non-diabetic patients (n=120)

Plaque type	Diabetic patients	Non-diabetic patients	p
Calcified	91 patients (86.67%)	51 cases (68%)	0.016
Mixed	74 cases (70.47%)	63 cases (84%)	
Noncalcified	41 cases (39.05%)	34 cases (45.33%)	
Ulcerated	2 cases (1.9%)	1 case (1.33%)	
Thrombotic	1 case (0.95%)	0 cases	

Regarding plaque composition, there was identified a statistically significant higher prevalence of calcified plaques in the diabetic group (p=0.016), a situation anticipated by the higher rate of calcium score. Mixed and non-calcified plaques were more frequently accounted in non-diabetic patients (Table 5).

Vulnerable plaques (non-calcified, ulcerated, thrombotic) were found in 45 diabetic patients (42.86%) and in 35 non-diabetic patients (46.67%)

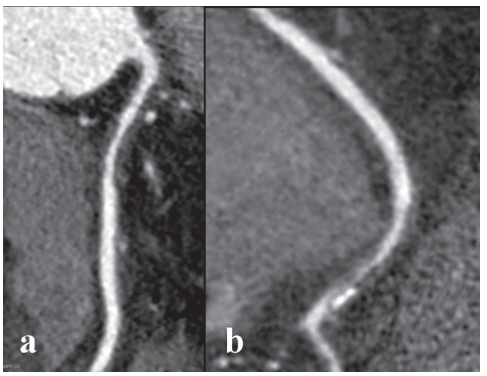

Figure 2. Coronary plaques in a diabetic patient: a. 50% coronary stenosis caused by a non-calcified plaque with positive remodeling in the 1st segment of the right coronary artery; b. 90% coronary stenosis caused by a mixed plaque in the 3rd segment of the right coronary artery.

with no significant difference between the two groups.

The prevalence of significant coronary stenoses, defined by ≥50% luminal narrowing, was higher in diabetic patients (53 cases, 50.48%) compared to non-diabetic patients (29 cases, 38.67%) (p=0.008) (Fig. 2).

DISCUSSION

CAD, often asymptomatic in diabetic patients, is a worldwide leading cause of morbidity and mortality. Though diabetic patients without typical symptoms display at least an intermediate probability of CAD, they might present directly with ACS, as CAD can manifest clinically only in advanced stages.

Diabetic patients are at a higher risk of ACS and are usually diagnosed in advanced stages partially due to their neuropathy (insensitive to symptoms of CAD) and higher prevalence of significantly stenotic plaques.

Detection of CAD at an early stage in diabetic patients becomes both crucial and challenging. Currently, there is no consensus in the literature on the diagnostic method to be used for early detection of CAD. Systematic screening in asymptomatic high-risk cardiovascular patients is still a debatable subject.

MDCT has facilitated the noninvasive study of the coronary arteries in patients with chest pain and in those at risk of CAD through the quantification of coronary calcification (the Agatson calcium score) and the angiographic evaluation after contrast agent injection.

Several studies suggested that the risk of acute coronary syndrome (ACS) in asymptomatic diabetic patients is similar to the one registered in symptomatic nondiabetic patients (5, 6). Many clinical trials addressed the issue of improving event-free survival rate in people with DM and clinical CAD, but fewer studies dealt with the prevention and early diagnosis of CAD before appearance of clinical symptoms (7).

In the current study, diabetic patients had a different risk profile compared to non-diabetic ones, as their prevalence of arterial hypertension, dyslipidemia, and obesity was significantly higher, results explained by the strong association of metabolic syndrome with DM. There were found no significant differences concerning the lipidic profile between the two study groups, which suggests a good metabolic control of DM.

Anand *et al.* proved higher incidence of scintigraphic myocardial perfusion abnormalities in asymptomatic

diabetic patients with higher calcium scores, nearly 1/3 of patients with a calcium score higher than 400 having large ischemic defects (8).

Agatston calcium score was higher in diabetic patients (350.3±215.7) compared to non-diabetic patients (158.7±237.2). More than half of the diabetic patients (63.81%) presented moderate or severe coronary calcifications in contrast to only 34.67% of the non-diabetic patients, results consistent with those previously published by Raggi *et al.* and Qu *et al.* (9, 10). The coronary calcification score is strongly associated with mortality (as it has been thoroughly described in a review published by Thompson *et al.*) but a 0 calcium score cannot exclude the presence of coronary plaques as there can be patients with only noncalcified plaques (11).

In the present study, coronary plaques were identified in 87.5% of the diabetic patients and in 62.5% of the non-diabetic patients, the prevalence being significantly different. Similar findings in diabetic patients were reported by Kamimura *et al.* (81.19%), Hadamitzky *et al.* (86%) and Patel *et al.* (80.2%) (12-15). The prevalence of significant coronary stenoses was higher in diabetic patients (50.48%) compared to non-diabetic patients (38.67%). In the reviewed literature we found a variable rate of 30-56.3% significant coronary stenoses (≥50%) in asymptomatic diabetic patients (13, 15). Hadamitzky *et al.* found that only 30% of coronary plaques determined a ≥50% stenosis in his group of 140 diabetic patients without known CAD (13).

Both diabetic and non-diabetic patients analyzed in the current study had two or more affected vessels. A particular aspect noted in diabetic patients was the higher rate of diffuse involvement extending to the distal part of the vessels. LAD was the most affected artery in the two groups.

Analyzing the plaque composition, we observed a significantly higher prevalence of calcified plaques in the diabetic group (86.67%), as expected given the higher mean of calcium score. Surprisingly, we accounted more mixed plaques in non-diabetic patients (45.33%) as opposed to diabetic patients (39.05%). Pundziute *et al.* suggested a more rapid evolution of atherosclerosis in diabetic patients associated with a faster transition from noncalcified to calcified plaques (16). However, we found no differences when comparing the prevalence of vulnerable and non-vulnerable plaques between the two groups.

There is uncertain if diabetic patients present a high risk of coronary accident due to their insensitivity to coronary artery disease or secondary their prevalence of nonobstructive high risk plaques. Goraya *et al.* suggested that a higher calcified plaques burden in diabetic patients could be explained by the advanced glycation end products inducing the expression of genes and enzymes involved in the active calcification processes that occur in atherosclerotic plaque formation (17). Hyperglycemia also induces osteopontin (a calcium-binding, phosphorylated glycoprotein that acts like a bridge between cells and minerals) expression

in smooth muscle cells of the vascular wall. Besides being implied in plaque calcification, osteopontin is also involved in plaque progression by promoting further platelet function abnormalities. Therefore, sustained hyperglycemia acts as a proatherogenic and prothrombotic factor that ultimately results in plaque calcification (18).

Given the fact that myocardial perfusion imaging studies are of limited access in our country, CCTA could be used as a screening method for identifying asymptomatic diabetic patients at risk for major cardiac events as it can rule out with high accuracy obstructive CAD.

Study limitation

The current study was performed in a single centre, it was not designed as a cross-sectional one and was limited to a specific geographical area. The patients enrolled in the study group presented plurifactorial coronary microvascular risk factors, such as diabetes, cigarette smoking, dyslipidaemia and hypertension, facts that might suggest the possibility of false-positive results. The current approach based on image information representing anatomical rather than functional aspects can under- or overestimate the impact of CAD, thus probably explaining the lack of correlation between detected lesions and asymptomatic CAD observed in our study.

In conclusion, asymptomatic diabetic patients display an increased prevalence of CAD compared to non-diabetic patients, more than half of asymptomatic diabetic patients having significant coronary stenosis. Given the high prevalence of CAD among asymptomatic diabetic patients, CCTA could represent a possible screening method able to accurately detect silent atherosclerotic plaques, thus contributing to prevention of ACS by establishment of an early and adequate treatment. The ability of CCTA to recognize significant coronary lesions limits the use of more invasive imaging methods such as coronary angiography and selects patients that could benefit of coronary revascularization.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

Cardiovascular diseases (CVD), Coronary artery disease (CAD), Multidetector Computed Tomography (MDCT), acute coronary syndrome (ACS), coronary computed tomography angiography (CCTA), Diabetes Mellitus (DM), World Health Organization (WHO).

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