

The association between extracoronary calcification and coronary artery disease in patients with type 2 diabetes mellitus

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Abstract Cardiovascular complications are the major cause of diabetes-associated morbidity and mortality. However, not all patients with diabetes are at increased risk for cardiovascular disease (CVD). Coronary artery calcification was found to be a powerful predictor of coronary artery disease (CAD). The presence of extracoronary cardiac calcification as a useful predictor of CAD is not yet established, especially in type 2 diabetes mellitus (T2DM). The aim of this study was to evaluate the relation between extracoronary calcification and extent of CAD in a group of T2DM patients who were scheduled for computed tomographic coronary angiography (CTCA). We prospectively studied 380 patients (151 had T2DM) under the age of 60 years who were scheduled for CTCA because of suspected CAD. Severity of CAD was assessed by Gensini score. Coronary artery calcium score (CACS) as well as calcium score in the aortic valve, mitral annulus, ascending aorta, and descending aorta were measured by a 256-row multidetector computed tomography scanner with dedicated software for calcium calculation. Patients with known CAD were excluded. Diabetic and nondiabetic patients had comparable age and gender distribution. However, the diabetic group had higher Gensini score, CACS, and extracoronary calcium score (ECCS). Logistic regression analyses identified male gender and ECCS as

significant predictors for the presence of CAD in diabetic patients. Age, smoking, and ECCS were the significant predictors of CAD in nondiabetic patients. Type 2 diabetic patients had increased coronary and extracoronary calcification. ECCS was found to be a significant predictor of CAD in diabetic and nondiabetic patients only when CACS was not taken into account.

Keywords Extracoronary calcification ·
Coronary artery disease · Diabetes

Introduction

Cardiovascular disease (CVD), especially coronary artery disease (CAD), is the most common complication and the principal cause of death in type 2 diabetes mellitus (T2DM) [1]. Standard coronary risk factors appear to carry greater significance in diabetic patients [2, 3]. However, other markers such as coronary calcification seem to provide a potential predictor of CVD events. This adds incremental value to conventional risk factors and risk scores both in the general population and in patients with T2DM [4–8]. There is also emerging evidence indicating that calcification involving heart valves and thoracic aorta is a manifestation of generalized atherosclerosis [9–11]. Few studies have shown that assessing the presence and extent of extracoronary calcification may improve prognostic information in subjects who are at risk for CVD [12, 13].

While previously published reports have demonstrated, in limited samples of diabetic individuals, greater burden of calcified coronary plaques as compared with nondiabetic individuals [14–16], at present there are no data regarding whether diabetic patients also have a greater burden of extracoronary calcification.

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We hypothesized that extracoronary calcific burden may represent a useful additional marker for risk assessment in T2DM patients. The aim of this study was to evaluate the relation between extracoronary calcification and extent of CAD in T2DM patients under the age of 60 years who were scheduled for computed tomographic coronary angiography (CTCA).

Patients and methods

Subjects

We prospectively studied 151 T2DM patients <60 years old and 229 age- and sex-matched nondiabetic patients who were scheduled for CTCA because of equivocal results of stress testing or the presence of multiple cardiovascular risk factors. All patients were in normal sinus rhythm and were free of clinical CVD (history of myocardial infarction, unstable angina, stroke, or previous coronary revascularization).

The traditional cardiovascular risk factors including hypertension, T2DM, smoking, and dyslipidemia were evaluated. In addition, body mass index (BMI) was calculated for all patients enrolled according to the following formula: $BMI = \text{body weight in kg/height (m}^2\text{)}$. Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg and/or use of antihypertensive medications. Diabetes mellitus was defined as fasting plasma glucose level >126 mg/dl and/or use of blood glucose-lowering medications. Dyslipidemia was defined as serum cholesterol >200 mg/dl, and/or high-density lipoprotein cholesterol <40 mg/dl and/or use of lipid-lowering medications. Smokers were defined as those who were currently smoking or had quit within the last 5 years. Obesity was defined as $BMI \geq 30$.

Clinical exclusion criteria were type 1 diabetes mellitus, age ≥ 60 years, renal failure (creatinine >1.5 mg/dl), known allergic reaction to contrast media, and valvular heart disease (rheumatic heart disease, degenerative mitral or aortic valve disease, or valve prosthesis).

The study protocol was approved by the local ethics committee, and all patients gave informed consent.

Multidetector computed tomography

Multidetector computed tomography (MDCT) was performed by using an iCT 256 (Philips Medical Systems; Eindhoven, the Netherlands) scanner. Cardioselective β -blocker (metoprolol 50–100 mg orally) was administered 1 h prior to the MDCT scan in patients with heart rate >70 beats/min.

After a low dose of precontrast scan (Collimation, 256×0.625 mm, gantry rotation time 270 ms, tube voltage 120 kV, current 80 mA) with simultaneously recorded electrocardiograph signal, a bolus of 70–80 ml of nonionic contrast (ultravist 370; Schering, Berlin, Germany) was injected through an 18-gauge cannula into the antecubital vein (flow rate of 5–6 ml/s) using a programmed dual-head injector pump (MEDRAD, Warrendale, PA, USA). This was followed by injection of 40 ml of chasing saline to push the injected contrast material. The semiautomated determination of the starting time using the “Bolus tracing technique” utilizing the Bolus-tracking program (Philips Medical Systems) was performed in all patients.

The following scan protocol was used: collimation 256×0.625 mm, craniocaudal direction, rotation time 270 ms, tube voltage 120 kV (increased to 140 kV in obese patients), and tube current 550 ± 150 mA. All scans could be performed within one single breath-hold (8–10 s).

For image reconstruction, the volume data set for coronary artery visualization was acquired in a spiral mode with simultaneous acquisition of 256 parallel slices. The field of view was 25 cm with an image matrix of 512×512 pixels. Two data sets were created during different time instants of the cardiac cycle (40% and 75% of the RR interval), with more image sets created at different phases of the cardiac cycle when needed.

The data set containing the fewest motion artifacts was used for further creation of the reconstructed images and evaluation of coronary arteries. The reconstructed axial images at different points of cardiac cycles were sent to a remote work station (Vitea2; Vital Images, Minnetonka, MN, USA) for off-line analysis.

Calcium scores were calculated with the dedicated software and expressed as volumetric and Agatston scores. Using the sequential axial images, any tissue above 130 HU occupying a minimum of 0.5 mm^2 that could be identified along the anatomical course of a coronary artery was considered as coronary artery calcification, and hence, highlighted and analyzed. Similarly, calcification of the aortic and mitral valves as well as the ascending and descending thoracic aorta were identified and calculated separately. Calcification was attributed to the aortic and mitral valves if it was clearly part of the valve cusps or annulus. Calcification of the aorta was defined as the presence of at least one detectable lesion of calcified deposit within the area of the aortic wall. Coronary artery calcium score (CACS), extracoronary calcium score (ECCS), which is the sum of calcium scores in the aortic valve, mitral annulus, ascending and descending thoracic aorta, as well as total calcium score (TCS), which is the sum of CACS and ECCS, were calculated for all patients.

Image analysis

Computed tomographic coronary angiography was evaluated by Gensini score [17] to assess the extent and severity of CAD.

The Gensini score was computed by assessing the severity score of each coronary stenosis according to the degree of luminal narrowing and its geographic importance. Reduction in the lumen diameter and appearance of concentric lesion or eccentric plaques were evaluated (reduction of 25%, 50%, 75%, 90%, 99%, and complete occlusion were given Gensini scores of 1, 2, 4, 8, 16, and 32, respectively). Each vascular segment was assigned a multiplier in accordance with the functional significance of the myocardial area supplied by that segment: the left main coronary artery, $\times 5$; the proximal segment of left anterior descending artery (LAD), $\times 2.5$; the proximal segment circumflex artery, $\times 2.5$; the mid segment of the LAD, $\times 1.5$; the right coronary artery, the distal segment of LAD, the posterolateral artery, and the obtuse marginal artery, $\times 1$; and others, $\times 0.5$.

Statistical analysis

Numeric values are described as mean \pm SD. Categorical data are presented as absolute frequencies and percentages. The Pearson chi-square test was used to compare categorical data. Student's *t* test was performed to evaluate differences between diabetic and nondiabetic groups. Pearson's correlation coefficients were calculated to evaluate the relationship between calcium scores (coronary and extracoronary) and Gensini score as well as duration of diabetes. Logistic regression analysis was applied to determine which of the parameters were the significant variables associated with the presence of CAD (Gensini score >0) through two models. The first model was conducted for the whole studied population. The following variables were entered into the model: age, gender, BMI, smoking, T2DM, hypertension, dyslipidemia, CACS, and ECCS. Model 2 was applied for diabetic and nondiabetic groups separately, and included all variables in model 1 except T2DM and CACS. Both CACS and ECCS were examined as stratified variables (absence/presence). Values of $P < 0.05$ were considered statistically significant. All statistical analyses were performed with the SPSS 14.0.1 program (SPSS, Chicago, IL, USA).

Results

The study group consisted of 380 consecutive patients scheduled for CTCA. Demographic and clinical characteristics for the diabetic and nondiabetic groups are

summarized in Table 1. Both groups had comparable age and gender distribution; however, diabetic patients had greater prevalence of hypertension and dyslipidemia and they had higher BMI. Frequency of smoking in the diabetic group was less than in the nondiabetic group. All diabetic patients were receiving blood glucose-lowering medications; 88 (58.3%) received oral hypoglycemic drugs (sulfonylureas and/or biguanides) and 63 (41.7%) received insulin therapy.

Multidetector computed tomography findings

Normal coronary arteries without evidence of coronary plaques in CTCA were found in 19.2% of diabetic patients compared with 44.1% of the nondiabetic group ($P < 0.000$). As shown in Table 2, diabetic patients had higher Gensini score, CACS, aortic valve calcium (AVC), ascending aorta calcium (AAC), descending aorta calcium (DAC), ECCS, and TCS. There was no significant difference between both

Table 1 Demographic and clinical characteristics of diabetic and nondiabetic patients

	T2DM (<i>n</i> = 151)	No DM (<i>n</i> = 229)	<i>P</i> value
Age (years)	55 \pm 4	54 \pm 5	0.103
Male gender (%)	86 (57)	140 (61)	0.455
BMI (kg/m ²)	31.7 \pm 4.3	29.3 \pm 3.2	<0.000
Obesity (%)	69 (46)	112 (49)	0.600
Smoking (%)	54 (36)	109 (48)	0.026
Duration of DM in years	6.2 \pm 5.6	–	–
Hypertension (%)	124 (82)	160 (70)	0.008
Dyslipidemia (%)	125 (83)	147 (64)	0.001

T2DM Type 2 diabetes mellitus, BMI body mass index

Table 2 Multidetector computed tomography data for diabetic and nondiabetic patients

	T2DM (<i>n</i> = 151)	No DM (<i>n</i> = 229)	<i>P</i> value
Gensini score	21.4 \pm 28.4	8.8 \pm 11.7	<0.000
CACS	147 \pm 232	61 \pm 143	<0.000
AVC	46 \pm 123	18 \pm 85	<0.000
MAC	8 \pm 62	4 \pm 32	0.063
AAC	42 \pm 138	22 \pm 78	<0.000
DAC	90 \pm 325	28 \pm 118	<0.000
ECCS	186 \pm 439	72 \pm 202	<0.000
TCS	333 \pm 550	133 \pm 273	<0.000

T2DM Type 2 diabetes mellitus, CACS coronary artery calcium score, AVC aortic valve calcium, MAC mitral annulus calcium, AAC ascending aorta calcium, DAC descending aorta calcium, ECCS extracoronary calcium score, TCS total calcium score

groups for mean mitral annulus calcium (MAC). ECCS >0 was found in 99 (65%) diabetic patients compared with 76 (33%) of the nondiabetic group ($P < 0.000$).

Pearson's correlation analysis

There was a significant correlation between CACS and Gensini score ($r = 0.374$, $P < 0.000$). Only AVC and DAC were weakly correlated with Gensini score ($r = 0.107$, $P = 0.037$) for both. A positive correlation was shown between CACS and the duration of diabetes ($r = 0.262$, $P = 0.001$); however, ECCS failed to show such a significant correlation.

Logistic regression analysis

For the whole studied population, model 1 (Table 3) identified T2DM (odds ratio (OR) 2.59, 95% confidence interval (CI) 1.2–5.5, $P = 0.013$), smoking (OR 2.48, 95% CI 1.1–5.6, $P = 0.028$), and CACS (OR 1.4, 95% CI 1.2–1.6, $P < 0.000$) to be independent predictors of CAD.

Table 3 Logistic regression analysis of predictors of CAD in the whole studied population

	All studied population ($n = 380$)	
	OR (95% CI)	P value
Age	1.03 (0.96–1.12)	0.411
Male gender	1.16 (0.51–2.60)	0.725
BMI	1.03 (0.93–1.13)	0.575
Smoking	2.48 (1.10–5.59)	0.028
Hypertension	1.28 (0.58–2.83)	0.548
T2DM	2.59 (1.22–5.51)	0.013
Dyslipidemia	1.25 (0.61–2.56)	0.538
CACS	1.40 (1.20–1.64)	<0.000
ECCS	1.00 (1.00–1.01)	0.089

BMI body mass index, *T2DM* type 2 diabetes mellitus, *CACS* coronary artery calcium score, *ECCS* extracoronary calcium score, *OR* odds ratio, *95% CI* 95% confidence interval

Table 4 Logistic regression analyses of predictors of CAD in T2DM patients and nondiabetic patients

	T2DM		No DM	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.11 (0.97–1.26)	0.124	1.12 (1.04–1.19)	0.002
Male gender	3.68 (1.13–12.00)	0.030	1.95 (0.96–3.94)	0.065
BMI	1.06 (0.94–1.20)	0.370	1.09 (0.99–1.20)	0.073
Smoking	1.60 (0.93–5.93)	0.485	2.71 (1.36–5.37)	0.004
Hypertension	0.38 (0.08–1.83)	0.227	1.45 (0.75–2.80)	0.273
Dyslipidemia	1.55 (0.44–5.45)	0.494	1.35 (0.71–2.56)	0.365
ECCS	1.03 (1.01–1.05)	0.007	1.00 (1.00–1.01)	0.026

T2DM type 2 diabetes mellitus, *BMI* body mass index, *ECCS* extracoronary calcium score, *OR* odds ratio, *95% CI* 95% confidence interval

The ECCS failed to show significant association with CAD (OR 1.00, 95% CI 1.00–1.01, $P = 0.089$). On the other hand, model 2 (Table 4) identified male gender (OR 3.68, 95% CI 1.3–12.0, $P = 0.030$) and ECCS (OR 1.03, 95% CI 1.01–1.05, $P = 0.007$) as variables significantly associated with CAD in diabetic patients. Age (OR 1.12, 95% CI 1.04–1.19, $P = 0.002$), smoking (OR 2.71, 95% CI 1.36–5.37, $P = 0.004$), and ECCS (OR 1.0, 95% CI 1.00–1.01, $P = 0.027$) were the significant predictors for the presence of CAD in nondiabetic patients.

Discussion

Extensive evidence in the literature exists that the risk of CAD is 2–5 times greater in patients with T2DM than in those free of the disease [18]. However, a recent meta-analysis of cohort or observational studies with hard clinical end points (fatal and nonfatal myocardial infarction) did not support the concept that T2DM is CAD equivalent [19]. The PREDICT study [20] had showed heterogeneity in cardiovascular risk from low to high in T2DM patients and that not all diabetic patients were at increased risk for CVD.

Since there is still controversy in this area, our investigation sought to determine whether extracoronary calcification (as an additional marker for CVD) might be useful in identifying high-risk patients with T2DM in whom preventive therapy could be started earlier than might otherwise be considered.

The major findings of this study are: (1) T2DM patients had greater scores of coronary and extracoronary calcification compared with age- and sex-matched nondiabetic subjects; (2) extracoronary calcification was a significant predictor of CAD with slightly higher odds in diabetic patients compared with nondiabetic patients, though this no longer persisted once CACS were taken into account; (3) CACS, AVC, and DAC had a significant correlation with Gensini score; (4) ECCS failed to show significant correlation with the duration of diabetes, although CACS had a weak positive correlation.

Our results of increased coronary calcification with diabetes are consistent with the current understanding of the pathophysiology of atherosclerosis, which is accelerated in patients with T2DM. Schurgin et al. [14] examined the degree of CACS in a sample of 139 asymptomatic diabetic individuals in comparison with a randomly selected nondiabetic group. Among diabetic subjects, 26% had scores ≥ 400 compared with 7.2% in the randomly selected nondiabetic patients. A larger study by Hoff et al. [16] showed that young diabetic individuals appear to have calcified plaque burden comparable with that of older individuals without diabetes.

While multiple studies have demonstrated an association between extracoronary calcification and angiographically defined CAD in the general population, to best of our knowledge very few studies have addressed this issue in patients with T2DM. Khoury et al. [21] found that extracoronary plaque in the descending aorta showed the strongest relation with obstructive CAD. Yamamoto et al. [12] showed that the presence of AVC and thoracic aortic calcification as detected by electron-beam computed tomography were associated with angiographic extent and severity of CAD and added incremental diagnostic value to the CACS. Adler et al. [22] found the prevalence of three-vessel obstructive CAD to be significantly higher in patients with echocardiographically detected MAC compared with patients with no MAC. Jeon et al. [23] studied 338 subjects ≤ 65 years old who underwent evaluation of chest pain with myocardial perfusion single-photon emission computed tomography and a two-dimensional transthoracic echocardiogram. The study showed that multiple calcific deposits at mitral annulus, aortic valve, and aortic root had significant discriminative power in identifying CAD when associated with multiple coronary risk factors or diabetes mellitus.

In fact, ECCS was also studied to determine its validity as predictor of CVD events in various types of population. Aortic arch calcium as measured by chest X-ray was shown to be an independent predictor of CVD events in hemodialysis patients [24]. In a recently published study with an 18-year follow up, investigators found marked thoracoabdominal calcification of native radiogram predicted CVD and total mortality, especially in nondiabetic and T2DM women [25]. Another recent study [26] indicated that thoracic aorta calcium as measured by computed tomography was a significant predictor of future coronary events only in women. However, when CACS was a contributor in the model, the significance was lost for both men and women. Our results showed that ECCS lost its significant association as a predictor of CAD when CACS was taken into account. This could be partly explained by the small sample size and partly by the fact that near 35% of the studied population had normal CTCA (Gensini score 0).

It is known that vascular calcification is initiated by metabolic, mechanical, or inflammatory injury to the

vasculature. Its progression is mainly determined by inflammatory response to vascular injury [25]. It may precede CVD morbidity and mortality by years or decades in subjects with T2DM [27]. To the best of our knowledge, the relationship of calcium in the coronary or extracoronary sites and duration of T2DM was not clearly discussed in the literature. However, Mineoka et al. [28] showed the relationship between the cardio-ankle vascular index (an arterial stiffness parameter) and CACS was greater in patients with advanced diabetic retinopathy and diabetic nephropathy (both reflect longer diabetes duration). The relatively young age group of our study population (55 ± 5 years) and the relatively short period of diabetes (6.2 ± 5.6 years) may explain our results of a weak correlation between CACS and duration of diabetes, and the failure of ECCS also to achieve a significant correlation.

Over the past few years numerous studies have shown that CTCA has emerged as a safe, noninvasive, patient-friendly diagnostic modality to detect the presence of coronary atherosclerosis [29]. Modern MDCT scanners allow assessment of coronary arteries in diabetic patients, with good sensitivity and specificity [30]. It is now routinely performed as a filter test for demonstrating or excluding CAD in patients with a low to intermediate pretest probability of CAD [31] and hence, measurement of CACS is becoming more widely available. We think that measurement of ECCS in addition may improve prognostic information without extra cost or further radiation exposure, especially in T2DM patients who are potential candidates for CVD.

Limitations

Because of the small sample size, there may not have been sufficient power to demonstrate that some coronary risk factors were predictive of CAD. A larger patient number is required to re-evaluate our results. We evaluated ECCS in the aortic valve, mitral annulus, and ascending and descending thoracic aorta as being easily measured during performance of CTCA. We did not evaluate the abdominal aorta, which is the main location for atherosclerosis, only to decrease exposure to ionizing radiation. Although Gensini score is one of the most comprehensive scoring systems for assessing the severity of coronary atherosclerosis, it might underestimate early lesions as well as lesions with outward remodeling, especially in diabetic patients.

Conclusion

This study showed that T2DM patients had increased coronary and extracoronary calcification. The ECCS was found to be a significant predictor of CAD in diabetic and

nondiabetic patients only when CACS was not taken into account. The increasing use of MDCT in clinical practice may enhance the utility of ECCS, in addition to CACS, to be a useful measure in the stratification of at-risk diabetic patients into a more aggressive management plan.

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