Coronary artery calcium in type 2 diabetes: a nested case-control study

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INTRODUCTION
The use of classic risk scores in patients with type 2 diabetes have numerous limitations. Relationships between coronary artery calcium score (CACS) and traditional risk factors are derived from statistical analyses. At present, there are no data on the evaluation of the CACS on 64-slice multi-detector computed tomography in patients with type 2 diabetes and ischemic symptoms based on a head-to-head comparison with matched nondiabetics.

OBJECTIVES
We aimed to examine the associations between traditional risk factors and the CACS in a nested case-control study.

PATIENTS AND METHODS
We performed a retrospective analysis of data from 2482 consecutive symptomatic subjects with known CACS. We identified 325 patients with type 2 diabetes. From the remaining subjects, 325 controls matched for age, sex, and risk factors were selected.

RESULTS
Higher CACS values were observed in patients with diabetes (median, 50 Agatston units [AU]; range, 0–4330) compared with nondiabetic controls (9 AU, 0–3036, \( P < 0.001 \)). Positive CACS values were more common in diabetic patients (73.5%) compared with nondiabetic controls (60.9%, \( P < 0.001 \)). The highest CACS value was observed in men (95.5 AU, 0–3755). The median CACS value in nondiabetic men was comparable to those in diabetic women (24.5 AU, 0–3036 vs. 24.5 AU, 0–3755). The lowest CACS values were observed in control women (3 AU, 0–2144). Coronary artery calcium was more diffused in diabetic patients compared with controls (\( P < 0.01 \)). A multivariate analysis showed that older age and male sex were independent predictors of the CACS. Traditional risk factors accounted only for 10% of interindividual variance in the presence of calcified atherosclerotic plaques.

CONCLUSIONS
Coronary calcified lesions are more frequent in symptomatic patients with type 2 diabetes compared with matched nondiabetic subjects. Our results seem to provide evidence that traditional risk factors do not explain more common, diffuse, and extensive calcified lesions in diabetic subjects.
CAD (typical and atypical angina, angina equivalents, or nonanginal chest pain).

The coronary artery calcium score (CACS) is a unique, direct marker of coronary atherosclerosis. It can be determined in vivo in either asymptomatic or symptomatic subjects by means of fast electron-beam computed tomography (EBCT) or multidetector computed tomography (MDCT). The CACS has been shown to be a predictor of CAD-related and all-cause mortality in nondiabetic subjects with the predictive power far beyond the standard risk factors used in risk scores. It was demonstrated that the measurement of the CACS by EBCT allowed to predict all-cause mortality equally well in patients with diabetes and in nondiabetic subjects. In a prospective study in type 2 diabetic patients with silent myocardial ischemia in West London, United Kingdom, the CACS was found superior to common risk factors as a predictor of coronary events. In another large prospective cohort study in type 2 diabetes (PREDICT Study), the CACS enhanced cardiovascular risk prediction estimated by a classic factor analysis. Most studies on the association between the CACS and risk factors in type 2 diabetes have been conducted in asymptomatic populations, usually racially heterogeneous. Reports about CACS determination in symptomatic type 2 diabetic patients are rare. In our study, EBCT was used to calculate the CACS. Also, it was a cohort design study, biased by the inclusion of patients with indications for invasive coronary angiography. There are much more data on the use of MDCT coronary angiography in these patients.

Typically, the relationship between CACS and traditional or novel cardiovascular risk factors is derived from statistical analyses, usually a multivariate analysis. By using such an approach, predefined risk factors are added to a statistical model. Similar statistical evaluation is used in almost all studies involving diabetic patients. To our knowledge, there have been as few as 2 reports in which a nested case-control design was applied to EBCT-based CACS in asymptomatic type 2 diabetics compared with nondiabetic controls. At present, there are no data regarding the evaluation of the CACS on 64-MDCT in symptomatic type 2 diabetic patients with a head-to-head comparison with matched symptomatic non-diabetic subjects. Therefore, we aimed to examine the association between classic risk factors and the CACS in a study with a nested case-control design.

**PATIENTS AND METHODS**

**Study population**

We conducted a retrospective analysis of data from 2482 consecutive symptomatic subjects (897 men, 1585 women; mean age, 58 ±10 years; age range, 31–89 years), in whom the CACS was measured between June 2008 and April 2010. We selected 325 patients with known type 2 diabetes (106 men, 219 women; mean age, 60 ±9 years; age range, 35–87), who were diagnosed by their physician and were treated with insulin and/or oral agents. From the remaining subjects, we selected 325 individuals matched for age, sex, and the presence of at least 4 of 5 risk factors (smoking, hypertension, lipid disorders, family risk, and overweight/obesity). All patients were referred for CACS measurement by their physicians due to the presence of CAD-related symptoms (chest pain, dyspnea, arrhythmias). The exclusion criteria were as follows: high risk of CAD (according to the Diamond-Forrester scale >85%), age <35 years, type 1 diabetes, inability or refusal to sign consent, pregnancy or uncontrolled childbearing potential, atrial fibrillation or frequent premature depolarizations precluding accurate electrocardiogram (ECG) gating. The protocol of the study was approved by the local ethics committee. All subjects provided written informed consent.

**Coronary artery calcium score**

Coronary artery calcium (CAC) measurement was performed using a Toshiba 64-slice MSCT. The scans were taken with a breath held in inspiration, prospectively ECG-gated, with a slice thickness of 3 mm. The examinations were done with 120 kV and the tube current ranged from 200 to 400 mA depending on body habitus. The CACS was assessed using the method of Agatston et al. with the cutoff value above 130 Hounsfld units (HU) used to define calcification. Briefly, the lesion area was multiplied by a density factor derived from the maximal HU. The density factor was 1 for lesions with a maximum density of 130 to 199 HU; 2 for a maximum density of 200 to 299; 3 for 300 to 399 HU; and 4 for lesions with a maximum density of 400 HU or higher. All images were reviewed on a workstation (Vitrea 2.0, Vital Inst., United States). Standardized reporting format for CAC scoring (Agatston units, AU) was used by all readers. The reproducibility of the CACS in our laboratory has been reported elsewhere. The median effective dose for CAC scoring in our laboratory was 0.74 mSv (10–90 percentiles of 0.59–1.01).

**Risk factors**

In each subject, age, sex, body mass index (BMI), smoking habit, systemic arterial hypertension, high lipids, and family risk were recorded according to an institutional clinical risk assessment protocol. We differentiated between normal-weight (BMI <25 kg/m²), overweight (BMI, 25–29.9 kg/m²), and obese subjects (BMI ≥30 kg/m²). Smoking habit was categorized as current, former (anytime in the past), and never-smoking. Systemic arterial hypertension was recognized in subjects who were currently being treated with antihypertensive agents or who had already been diagnosed as hypertensive (irrespective of the use of medications), or in whom repeated measurements of blood pressure were 140/90 mmHg or higher. High lipids were recorded in subjects taking lipid-lowering drugs or who had documented total cholesterol
Positive coronary artery calcium score in diabetes

Significantly higher CACS values were observed in diabetic patients (median, 50 AU; range, 0–4330) compared with nondiabetic controls (9 AU, 0–3036) ($P < 0.001$). Moreover, we observed a significantly higher proportion of patients with positive CACS among symptomatic, type 2 diabetic patients (73.5%) compared with controls (60.9%) ($\chi^2$, $P < 0.001$). In diabetic patients, the CACS between 101 and 400 AU was reported in 20.8%, between 401 and 1000 AU in 11.1%, and above 1000 AU in 6.1%, while in nondiabetic patients the proportions were 17.6%, 5.5%, and 3.4%, respectively ($\chi^2$).

Coronary artery calcium score and sex

The greatest differences were found if the CACS values were compared between type 2 diabetic and nondiabetic women and men. The highest median value was observed in type 2 diabetic men (95.5 AU; range, 0–3755). The median CACS in nondiabetic men (24.5, range 0–3036) was as high as in diabetic women (24.5 AU, 0–3755). The lowest values were observed in nondiabetic women (3.0 AU, 0–2144).

Coronary artery calcium score and age

The effect of age was similar in symptomatic, diabetic subjects and their matched controls. However, at any age range (<50, 51–60, 61–70, and >70 years), the CACS was significantly higher in diabetics compared with controls only in women, while a less clear difference was observed in men older than 60 years of age (figure 3).

Extension of coronary artery calcium

There was a significant difference in CAC deposit location between diabetic and nondiabetic patients. CAC was more diffused in type 2 diabetic patients compared with matched controls ($\chi^2$, $P < 0.01$). As shown in figure 4, the involvement of 3 or more large epicardial vessels was more frequent in diabetic subjects regardless of age.

Correlation of coronary artery calcium score with risk factors

A multivariate linear regression analysis in nondiabetic patients showed that older age and male sex were the only independent predictors of CAC scoring with the $\beta$-coefficients of 0.30 and 0.26, respectively (both $P < 0.001$, $R^2 =$

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**TABLE** Characteristics of subjects by diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Type 2 diabetic patients</th>
<th>Nondiabetic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of patients (women/men)</td>
<td>325 (219/106)</td>
<td>325 (219/106)</td>
</tr>
<tr>
<td>age, y, mean ± 1SD</td>
<td>61.1 ± 8.2</td>
<td>61.1 ± 8.2</td>
</tr>
<tr>
<td>systemic arterial hypertension, n (%)</td>
<td>284 (87.3)</td>
<td>285 (87.6)</td>
</tr>
<tr>
<td>dyslipidemia, n (%)</td>
<td>185 (56.9)</td>
<td>184 (56.6)</td>
</tr>
<tr>
<td>smoking, n (%)</td>
<td>47 (14)</td>
<td>47 (14)</td>
</tr>
<tr>
<td>overweight or obesity (BMI &gt; 25 kg/m²), n (%)</td>
<td>291 (89.5)</td>
<td>278 (84.8)</td>
</tr>
<tr>
<td>positive CV family history, n (%)</td>
<td>190 (58.4)</td>
<td>189 (58.1)</td>
</tr>
</tbody>
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Abbreviations: BMI – body mass index, CV – cardiovascular, SD – standard deviation

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**FIGURE 1** Median values of coronary artery calcium score (CACS) in type 2 diabetic patients and matched nondiabetic controls (bars indicate median values, whiskers – 75 percentile, open dots – outliers)
0.108, \( F = 6.61 \). Among patients with type 2 diabetes, both these parameters were still significant with the \( \beta \)-coefficients of 0.22 (\( P < 0.001 \)) and 0.16 (\( P < 0.05 \)), respectively, but with a significantly lower \( R^2 \) value (0.091, \( F = 4.55 \)).

**DISCUSSION** Our study, conducted using a rare nested case-control design, confirmed the presence of the higher values of the CACS in symptomatic type 2 diabetic patients. In a head-to-head comparison with nondiabetic patients with the same prevalence of traditional risk factors, the proportion of type 2 diabetic patients with a positive CACS reached almost 75% and was higher than in nondiabetics. Moreover, the proportion of diabetic patients with the CACS between 400 and 1000 AU or above 1000 AU was twice higher than that of nondiabetics. Interestingly, the above differences were more pronounced in women, while in men aged 60 years and older, these differences were no longer observed. We also found that traditional risk factors were weak determinants of CAC both in type 2 diabetic and symptomatic nondiabetic patients, accounting for approximately 10% of individual variation of the CACS.

In a study by Wolfe et al.\(^{17}\) in 71 asymptomatic type 2 diabetics and in 71 controls matched for traditional risk factors, the median values of the CACS on EBCT reached 41 AU and 4 AU, respectively. These values were lower than those observed in our symptomatic patients both with type 2 diabetes and without diabetes. The use of different computed tomography scanners (MDCT vs. EBCT) might not explain the differences.\(^{20}\) On the other hand, Hosoi et al.\(^{13}\) reported that the median values of the CACS determined by means of EBCT were clearly higher in 101 asymptomatic Asian patients with type 2 diabetes and 181 nondiabetic patients scheduled for invasive coronary angiography, all of whom had significant coronary stenosis.\(^{13}\) However, it is important that indications for an invasive study and for CAC scoring in symptomatic subjects are quite different. Moreover, as shown by Mazzone et al.,\(^{21}\)
the presence of type 2 diabetes is equivalent to CAD, the evaluation of traditional risk factors in such a context does not pertain to CAC scoring, which is the simplest, direct, and unique method for atherosclerotic lesion detection within the coronary arteries.

The associations of risk factors are commonly established on the basis of a cross-sectional or cohort studies, which differ in terms of statistical adjustment and modeling. For example, 2 different reports from the PREDICT study provided conflicting results regarding correlation between age and the CACS. The results of our study might indicate that the significance of cross-sectional or cohort studies should be re-examined also in a nested case-control design study, in which no statistical corrections or modeling are necessary.

Study limitations The protocol used to assess the presence of traditional risk factors was based on self-reporting data. Such an approach has several limitations because the knowledge of patients, especially nondiabetic ones, about their own health is not objective. However, as part of routine examination, medical history is not only mandatory but in the case of symptoms remains the only source of detailed information before the laboratory data are obtained. Thus, a decision of whether to perform an invasive or noninvasive examination in symptomatic subjects is based more on the evaluation of symptoms and a patient’s history rather than on objective laboratory data.

We examined the sample in which the prevalence of definitively diagnosed type 2 diabetes reached 13.1%. This proportion is clearly higher than the incidence of diabetes in the general Polish population as well as the inhabitants of the Silesia province. Symptomatic status, older mean age, and higher BMI in patients with diabetes in our study might in part explain these differences.

We did not add the duration of diabetes to the panel of the examined factors. First, there are contradictory results concerning the association between the duration of diabetes and the CACS. Second, estimation of the actual duration of diabetes (for example, in contrast to smoking) is imprecise because patients may be asymptomatic for years and the true onset of type 2 diabetes cannot be determined. Finally, it was suggested that the angiographic rather than diabetic state determined prognosis in type 2 diabetic patients. In a recent study by Włodarczyk and Strojek, glucose metabolism abnormalities were observed commonly in 100 patients with stable CAD (44%); however, only obesity was recognized as the independent predictor of coronary atherosclerosis on invasive coronary angiography. In fact, in their study, only 9 of 100 patients were diagnosed as diabetic, while 35 patients with CAD were diagnosed with glucose intolerance. Due to a meaningful difference in the number of patients with...
type 2 diabetes (9 vs. 325 in our study) as well as a different design, the results of the 2 studies cannot be compared.

In our study, we did not mention the usefulness of CACS determination for a decision-making algorithm. Thus, the effect of CAC scoring both in symptomatic type 2 diabetics and nondiabetics on the management of patients is unknown. Accordingly, our results have to be verified in a properly designed clinical investigation. However, the results of our study clearly indicate that CAC scoring might be helpful in women, while the evaluation of traditional risk factors or diabetic status is of limited value in older symptomatic men.

We concluded that the CACS measured by MDCT was higher in symptomatic type 2 diabetic patients than in symptomatic nondiabetic controls matched for risk factors. The results of our study provide convincing evidence that traditional risk factors cannot explain more frequent, more diffuse, and extensive calcified lesions in diabetic subjects.

REFERENCES


ARTYKUŁ ORYGINALNY

Wskaźnik uwapnienia tętnic wieńcowych u chorych z cukrzycą typu 2 – zagnieżdżone badanie kliniczno-kontrolne

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STRESZCZENIE

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