Prevalence of Angiographically Defined Obstructive Coronary Artery Disease in Asymptomatic Patients with Type 2 Diabetes According to the Coronary Calcium Score

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Abstract

Objective The aim of this study was to determine whether the absence of coronary artery calcium (CAC) can safely exclude obstructive coronary artery disease (CAD) in asymptomatic patients with type 2 diabetes.

Methods We enrolled 478 consecutive asymptomatic patients with type 2 diabetes who visited the diabetes clinic of the Asan Medical Center between October 1, 2009 and December 31, 2010. All patients underwent 64-slice dual-source computed tomography (DSCT) for CAC scoring as well as computed tomography angiography (CTA). Patients with at least one significant coronary stenosis with >50% luminal narrowing were classified as having obstructive CAD. The findings were confirmed using conventional coronary angiography (CAG).

Results Among the 478 patients, 157 (33%) had a CAC score of 0 (CAC=0). Of these, 17 (11%) had obstructive CAD confirmed on CAG. The presence of CAC had a negative predictive value for obstructive CAD on CAG of 89% and a sensitivity of 88%, a specificity of 42% and a positive predictive value of 38%. A multivariate logistic regression analysis showed that current smoking habits were significantly associated with the presence of obstructive CAD in patients with CAC=0 after adjusting for traditional cardiovascular risk factors (odds ratio 4.87, 95% confidence interval 1.65-14.42, p=0.004).

Conclusion Our findings suggest that CAC=0 on 64-slice DSCT cannot safely exclude obstructive CAD on CAG in asymptomatic patients with type 2 diabetes, particularly in current smokers. CTA should be combined with CAC scoring in screening for CAD in asymptomatic patients with type 2 diabetes.

Key words: coronary artery calcium score, coronary artery disease, dual-source computed tomography, type 2 diabetes mellitus

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Introduction

Coronary artery disease (CAD) is the leading cause of mortality in patients with type 2 diabetes. Patients with both diabetes and CAD are often asymptomatic until the onset of acute coronary events (1) and have a poor prognosis (2). The use of an approach strategy guided by the number of CAD risk factors has been advocated (3); however, subsequent studies have demonstrated that advanced CAD is frequently found in patients with fewer risk factors (4, 5).

Coronary artery calcium (CAC) scoring has emerged as a promising tool for CAD risk assessment (6). The amount of CAC on cardiac computed tomography (CT) has been found to correlate with the total coronary atherosclerotic burden and the risk of adverse cardiovascular outcomes. A recent

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prospective study demonstrated that the CAC score is a significant independent predictor of CAD events and can enhance the predictive power of traditional cardiovascular risk factors in asymptomatic patients with diabetes (7).

Recently introduced cardiac CT scanners have enabled the combination of CAC scoring and computed tomography angiography (CTA) (8, 9). However, CTA has several limitations, such as a high cost, exposure to high-dose radiation and the use of iodinated contrast agents. Therefore, it is unclear whether all patients suspected of having CAD should be screened with these two modalities. In particular, it is uncertain whether a CAC score of 0 (CAC=0) can exclude a diagnosis of obstructive CAD. A meta-analysis of 18 studies showed that the presence of CAC has a negative predictive value for obstructive CAD of 93%, suggesting that CAC=0 can safely exclude obstructive CAD (10). Other studies have also shown that patients with CAC=0 have a very low risk of cardiac events during the follow-up (11, 12), thus suggesting that these patients do not need further evaluation with CTA. In contrast, a recent study suggested that CAC=0 cannot reliably rule out obstructive CAD in asymptomatic patients since a significant proportion of patients with CAC=0 have obstructive CAD (13). However, the ability of CAC=0 to exclude obstructive CAD in asymptomatic patients with type 2 diabetes has not yet been examined. We therefore examined whether CAC=0 can safely exclude obstructive CAD in asymptomatic patients with type 2 diabetes.

Materials and Methods

Patients

We enrolled 478 consecutive asymptomatic patients with type 2 diabetes who visited the diabetes clinic of the Asan Medical Center between October 1, 2009 and December 31, 2010. All patients underwent 64-slice dual-source computed tomography (DSCT) for CAC scoring as well as CTA. The exclusion criteria included: chest pain or angina-equivalent symptoms, as determined using the Rose angina questionnaire (14); abnormal resting electrocardiogram (ECG) findings, including pathological Q waves, ischemic (≥1 mm depression) ST segments, deep negative T waves or complete left bundle branch block; a previous history of myocardial infarction/angina or percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG); ventricular or supraventricular arrhythmia; an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m²; and a previous history of allergies to iodinated contrast agents.

Of the 478 eligible patients, 161 had at least one significant stenosis with >50% luminal narrowing on 64-slice DSCT (Fig. 1). These patients were recommended to undergo conventional coronary angiography (CAG) for confirmation of the 64-slice DSCT results. Four patients refused to undergo CAG: two had a CAC score of 101 to 400 and two had a CAC score of >400. Of the remaining 157 patients, 139 had obstructive CAD as confirmed on CAG. Of these patients, 73 underwent subsequent revascularization, 63 underwent PCI and 10 underwent CABG. All patients enrolled in this study provided their written informed consent. The study protocol was approved by the Institutional Review Board of the Asan Medical Center.

Clinical and biochemical assessment

The basic demographic data were acquired during personal interviews. All patients were asked about their history of angina, myocardial infarction, revascularization, age at diagnosis of diabetes, current smoking habits and current medication profiles. Type 2 diabetes was diagnosed according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (15). Hypertension...
was defined as a blood pressure ≥140/90 mmHg or the use of antihypertensive medications. Patients with low-density lipoprotein (LDL)-cholesterol ≥130 mg/dL, high-density lipoprotein (HDL)-cholesterol <40 mg/dL, total cholesterol ≥200 mg/dL, triglycerides ≥150 mg/dL or who were using lipid-lowering medications were classified as having dyslipidemia. Current smoking habits were defined as smoking currently or having stopped smoking within one year of the interview.

The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Blood pressure (BP) was measured on the right arm after a ≥5 minute rest using an automatic manometer with an appropriate cuff size. The levels of total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, fasting plasma glucose, glycosylated hemoglobin and serum creatinine were measured after a fast of at least 12 hours. The eGFR was calculated using the Modification of Diet in Renal Disease equation (16). A standard 12-lead ECG was recorded and scored centrally by an experienced ophthalmologist. The extent of albuminuria was determined from the albumin-creatinine ratio in a random spot urine collection. The presence of diabetic retinopathy was defined as microalbuminuria (30-300 μg albumin/mg creatinine) or overt albuminuria (>300 μg albumin/mg creatinine) in the absence of other conditions capable of causing proteinuria.

**Evaluation of CAC scores and coronary stenosis**

In all eligible patients, CAC measurement was followed immediately by CTA using a 64-slice DSCT scanner (Somatom Definition, Siemens Medical Solutions, Germany). Patients with baseline heart rates >85 beats/min were given oral beta-blockers before undergoing 64-slice DSCT imaging. Each patient was also given 0.6 mg of nitroglycerin sublingually one minute before undergoing 64-slice DSCT. A standard scanning protocol was utilized with 2×32×0.6 mm collimation, 64-slice acquisition per rotation, 330 ms rotation time, 100-120 kVp tube voltage and 250-380 mAs/rot tube current according to the patient’s body habitus. All scans were performed using ECG-gated dose modulation. A bolus of 60-80 mL of iomeprol (Iomeron 400; Bracco, Milan, Italy) was intravenously injected (4-5 mL/s) followed by a saline flush of 50 mL. A region of interest was defined on the ascending aorta, and image acquisition was automatically initiated once a selected threshold (120 Hounsfield units) was reached with bolus tracking. Each patient’s ECG was simultaneously recorded to allow for retrospective segmental data reconstruction. The images were initially reconstructed at the mid-diastolic phase (75% of the R-R interval) of the cardiac cycle. The average radiation dose for 64-slice DSCT was 4.5±1.8 mSv.

All scans were evaluated on a 3-dimensional image analysis workstation (Syngo Workstation; Siemens Medical Solutions, Germany). An experienced radiologist who was unaware of the patients’ clinical information calculated the CAC scores according to the Agatston method (17). All coronary CT angiograms were interpreted by a consensus of two experienced radiologists who were unaware of the patients’ clinical information and CAC scores. Each lesion was identified using a multiplanar reconstruction technique and the maximum intensity projection of short-axis, two-chamber and four-chamber views. Coronary artery stenosis and plaque characteristics were analyzed on a per-segment basis according to American Heart Association criteria (18). The contrast-enhanced portion of the coronary lumen was semi-automatically traced at the maximal stenotic site and compared with the mean values of the proximal and distal reference sites. Plaques were defined as structures >1 mm² within and/or adjacent to the vessel lumen. Plaques consisting of calcified tissue occupying more than 50% of the plaque area (density >130 HU in native scans) were classified as calcified plaques, plaques with <50% calcium were classified as mixed plaques and plaques without any calcium were classified as non-calcified plaques.

Patients with at least one significant coronary stenosis with >50% luminal narrowing on 64-slice DSCT underwent CAG within four weeks of undergoing index 64-slice DSCT. All conventional coronary angiograms were interpreted by an experienced cardiologist who was unaware of the results of the CAC scores and CTA. Patients with at least one significant coronary stenosis with >50% luminal narrowing on CAG (n=139) were classified as having obstructive CAD. Patients demonstrating maximal coronary stenosis with 1-50% luminal narrowing on 64-slice DSCT (n=156) or CAG (n=18) were classified as having non-obstructive CAD. Patients with normal coronary arteries on 64-slice DSCT (n=161) were classified as having no CAD. Revascularization procedures, such as PCI and CABG, were performed at the physician’s discretion depending on the results of CAG.

**Statistical analysis**

Continuous variables with a normal distribution are expressed as the mean ± SD, continuous variables with a skewed distribution are expressed as the median (and interquartile range) and categorical variables are expressed as the frequency (%). Patients were categorized into four groups based on their coronary artery calcium scores (0, 1-100, 101-400 and >400). The clinical and biochemical characteristics of these four groups were compared using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test for continuous variables and the chi-square trend test for categorical variables. The presence of coronary plaque (any, calcified, mixed, non-calcified) was analyzed on a per-patient basis. The prevalence of coronary plaque subtypes and obstructive CAD in the four groups according to the CAC
Table 1. Clinical and Biochemical Characteristics of Patients with Type 2 Diabetes According to Categorical CAC Scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>0 (n=157)</th>
<th>1-100 (n=151)</th>
<th>101-400 (n=92)</th>
<th>&gt;400 (n=78)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAC score (AU)</td>
<td>0 (n=157)</td>
<td>34 (8-64)</td>
<td>198 (148-278)</td>
<td>890 (543-1438)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 ± 8.1</td>
<td>62 ± 8.0</td>
<td>65 ± 6.9</td>
<td>67 ± 7.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>85 (54)</td>
<td>95 (63)</td>
<td>64 (70)</td>
<td>57 (73)</td>
<td>0.002</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>10.0 (5.0-15.0)</td>
<td>12.0 (7.0-17.0)</td>
<td>14.0 (9.0-20.0)</td>
<td>16.5 (11.8-22.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 ± 8.7</td>
<td>25 ± 13.3</td>
<td>25 ± 3.6</td>
<td>25 ± 2.9</td>
<td>0.232</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57 ± 36</td>
<td>83 ± 55</td>
<td>61 (66)</td>
<td>56 (72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>128 ± 15.6</td>
<td>132 ± 13.8</td>
<td>137 ± 16.1</td>
<td>139 ± 16.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76 ± 9.0</td>
<td>78 ± 9.2</td>
<td>79 ± 8.7</td>
<td>80 ± 9.4</td>
<td>0.004</td>
</tr>
<tr>
<td>Current smoking</td>
<td>30 (19)</td>
<td>39 (26)</td>
<td>22 (24)</td>
<td>19 (24)</td>
<td>0.357</td>
</tr>
<tr>
<td>Insulin use</td>
<td>17 (11)</td>
<td>26 (17)</td>
<td>18 (20)</td>
<td>22 (28)</td>
<td>0.001</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>23 (15)</td>
<td>37 (25)</td>
<td>22 (24)</td>
<td>28 (36)</td>
<td>0.001</td>
</tr>
<tr>
<td>Statin use</td>
<td>23 (15)</td>
<td>39 (26)</td>
<td>21 (23)</td>
<td>25 (32)</td>
<td>0.005</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>41 (26)</td>
<td>54 (36)</td>
<td>38 (41)</td>
<td>44 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>22 (14)</td>
<td>33 (22)</td>
<td>22 (24)</td>
<td>24 (31)</td>
<td>0.003</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.3 (6.6-8.1)</td>
<td>7.5 (6.6-8.5)</td>
<td>7.2 (6.5-8.2)</td>
<td>7.4 (6.7-8.6)</td>
<td>0.166</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>130.0 (114.5-156.0)</td>
<td>135.0 (123.0-156.0)</td>
<td>130.0 (111.3-155.0)</td>
<td>133.0 (118.0-159.3)</td>
<td>0.088</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>76 (48)</td>
<td>80 (53)</td>
<td>49 (53)</td>
<td>46 (59)</td>
<td>0.140</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>176.0 ± 35.1</td>
<td>175.0 ± 35.9</td>
<td>177.1 ± 36.5</td>
<td>172.8 ± 32.6</td>
<td>0.871</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>109.3 ± 30.4</td>
<td>108.2 ± 31.3</td>
<td>110.3 ± 31.9</td>
<td>106.6 ± 28.4</td>
<td>0.868</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>49.3 ± 11.7</td>
<td>48.2 ± 10.7</td>
<td>47.0 ± 10.9</td>
<td>47.6 ± 10.9</td>
<td>0.428</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>119.0 (85.0-164.5)</td>
<td>122.0 (91.0-174.0)</td>
<td>128.0 (100.5-168.5)</td>
<td>118.0 (89.0-156.0)</td>
<td>0.545</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>85.4 ± 17.2</td>
<td>82.2 ± 16.1</td>
<td>78.4 ± 14.5</td>
<td>76.9 ± 13.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SD, median (interquartile range), or n (%). AU: Agatston unit, BMI: body mass index, CAC: coronary artery calcium, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate: FPG: fasting plasma glucose; HbA1c: glycosylated hemoglobin, HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, SBP: systolic blood pressure.

Table 2. Prevalence of Coronary Plaque Subtypes in Patients with Type 2 Diabetes According to Categorical CAC Scores

<table>
<thead>
<tr>
<th>Plaques (per-patient)</th>
<th>Total (n=478)</th>
<th>0 (n=157)</th>
<th>1-100 (n=151)</th>
<th>101-400 (n=92)</th>
<th>&gt;400 (n=78)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any plaque</td>
<td>350 (73%)</td>
<td>40 (25%)</td>
<td>140 (93%)</td>
<td>92 (100%)</td>
<td>78 (100%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calculated plaque</td>
<td>268 (56%)</td>
<td>0 (0%)</td>
<td>107 (71%)</td>
<td>85 (92%)</td>
<td>76 (97%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mixed plaque</td>
<td>118 (25%)</td>
<td>0 (0%)</td>
<td>46 (31%)</td>
<td>33 (36%)</td>
<td>39 (50%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-calcified plaque</td>
<td>178 (37%)</td>
<td>40 (25%)</td>
<td>60 (40)</td>
<td>45 (49)</td>
<td>33 (42%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are expressed as n (%). AU: Agatston unit, CAC: coronary artery calcium.

The prevalence of obstructive CAD in the patients according to their categorical CAC scores is shown in Table 3. As expected, higher CAC scores were associated with a higher prevalence of obstructive CAD, as confirmed on CAG (p for trend <0.001). Seventeen of 157 patients (11%) with CAC=0 had obstructive CAD. Nine of these 17 patients (53%) were men, and their mean age was 61.2 ± 9.2 years. Obstruc-

scores were compared using the chi-square trend test. Univariate and multivariate logistic regression analyses were used to calculate the odds ratios of traditional cardiovascular risk factors to predict obstructive CAD on CAG in patients with CAC=0. A p-value of <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA).

Results

The clinical and biochemical characteristics of the patients categorized according to their CAC scores are shown in Table 1. Increased age, male gender, a longer duration of diabetes, the presence of hypertension, higher values of systolic and diastolic BP, current use of insulin, aspirin or statins, the presence of diabetic retinopathy or nephropathy and a reduced eGFR were each significantly associated with higher CAC scores. There were no significant differences in BMI, the prevalence of current smoking habits, the levels of glycosylated hemoglobin and fasting plasma glucose, the prevalence of dyslipidemia or lipid profiles among these groups.

The distribution of the 64-slice DSCT-detected coronary plaque subtypes according to the categorical CAC scores is shown in Table 2. Higher CAC scores were associated with a higher prevalence of each individual plaque subtype. In particular, non-calcified plaques were observed in 178 of the 478 patients (37%), including 40 of the 157 patients (25%) with CAC=0. Representative images of calcified, mixed and non-calcified plaques as detected on CTA are shown in Fig. 2.

The prevalence of obstructive CAD in the patients according to their categorical CAC scores is shown in Table 3. As expected, higher CAC scores were associated with a higher prevalence of obstructive CAD, as confirmed on CAG (p for trend <0.001). Seventeen of 157 patients (11%) with CAC=0 had obstructive CAD. Nine of these 17 patients (53%) were men, and their mean age was 61.2 ± 9.2 years. Obstruc-
Discussion

In the present study, we found that obstructive CAD on CAG was present in 17 of 157 (11%) patients with CAC=0. These findings suggest that CAC=0 cannot safely exclude obstructive CAD in asymptomatic patients with type 2 diabetes and that CTA should therefore be used in combination with CAC scoring as a screening tool for CAD.

As expected, we found that obstructive CAD correlated significantly with higher CAC scores. However, the ability of CAC scoring alone to detect obstructive CAD is limited because it cannot detect obstructive CAD caused by non-calcified plaques. Indeed, all 17 of our patients with CAC=0 and obstructive CAD on CAG had obstructive (>50% stenosis) non-calcified plaques on 64-slice DSCT. Non-calcified plaques are highly prevalent in patients with type 2 diabetes (19) and 37% of our asymptomatic patients with type 2 diabetes had non-calcified plaques. Moreover, of our patients with CAC=0, 25% had non-calcified plaques and 11% had obstructive non-calcified plaques. This finding is different from the results of a previous study performed in subjects without diabetes in which 64-slice CT detected a much lower prevalence of non-calcified plaques (6.5%) and obstructive non-calcified plaques (0.5%) in subjects with CAC=0 (20). Our results therefore reemphasize that significant coronary artery stenosis caused by non-calcified plaques frequently occurs in patients with type 2 diabetes, even in the complete absence of calcification.

Interestingly, a current smoking habit was significantly associated with the presence of obstructive CAD caused by non-calcified plaques in patients with CAC=0. This is in agreement with previous studies showing that smoking is a strong predictor of non-calcified plaque (21). Even though non-calcified plaque is thought to be a feature of early stage atherosclerosis (22), a considerable number of patients with acute coronary syndrome present with non-calcified plaques (23, 24). A prospective study showed that patients with non-calcified plaques have higher serum C-reactive protein concentrations indicative of vascular inflammation than those without non-calcified plaques (25). In contrast, coronary calcification is not associated with C-reactive protein (26). Therefore, active inflammatory processes may play important roles in the development of non-calcified plaques during early stage atherosclerosis, rendering the plaques vulnerable to rupture. Cigarette smoking has been shown to promote atherosclerotic plaque formation (27). In particular, free oxygen radicals derived from cigarette smoke can increase oxidative stress, and smokers have elevated concentrations of inflammatory markers (28). Therefore, our findings suggest that a current smoking habit may be closely associated with the early non-calcified stage of atherosclerotic plaque formation, probably through pro-inflammatory effects. The Atherosclerosis Risk in Communities Study showed that the effects of smoking on the progression of atherosclerosis are greater in patients with diabetes than in subjects without diabetes (29). A large impact of smoking-induced coronary artery damage in patients with diabetes may contribute to the formation and progression of non-calcified plaque burdens, even in the complete absence of calcification.
calcification.

This study has several limitations. First, since it was performed at a single university hospital in South Korea, our results may not be applicable to other ethnic groups. Second, patients with normal coronary arteries or nonobstructive coronary artery disease on 64-slice DSCT were not referred for CAG. However, 64-slice CT tends to overdiagnose lesions and has an extremely high ability to exclude obstructive CAD (8, 30). Therefore, performing CAG in patients with negative results on 64-slice DSCT would not have been justified.

In conclusion, our results suggest that CAC=0 cannot safely exclude obstructive CAD on CAG in asymptomatic patients with type 2 diabetes, especially in current smokers. CTA should therefore be combined with CAC scoring in screening for CAD in asymptomatic patients with type 2 diabetes.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

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Jaechan Leem and Eun Hee Koh contributed equally to this work.

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