Impact of Diabetes on Coronary Stenosis and Coronary Artery Calcification Detected by Electron-Beam Computed Tomography in Symptomatic Patients

KATSUNOBU YOSHIOKA, MD1 
MASAFUMI MIYAMOTO, MD1 
TETSUYA YAMAKITA, MD1 
TAKANORI HASEGAWA, MD1 
KEIKO YAMAGAMI, MD1 
TOSHIHIKO SATO, MD1 
MASAYUKI HOSOI, MD1 
TSUNEHIKO YAMAMOTO, MD1 
SATORU FUJI, MD1 
SHIBO TANAKA, MD1 
AKIRA ITOH, MD2 
KAZUO HAZE, MD2 
KATSUNOBU YOSHIOKA, MD1

OBJECTIVE — Ischemic heart disease is a pivotal complication for diabetic patients. Electron-beam computed tomography (EBCT) represents the only noninvasive method that allows for accurate quantification of coronary artery calcification that reflects underlying atherosclerotic disease. Although coronary calcium score (CCS) cut points that predict the presence of angiographic stenosis have been established in nondiabetic individuals, it is not known whether coronary calcifications in diabetic patients are associated with the presence of significant coronary stenoses. In this study, we evaluated the relationship between coronary calcifications and angiographic stenosis in symptomatic patients with or without type 2 diabetes.

RESEARCH DESIGN AND METHODS — In this study, 282 patients (204 men and 78 women) with chest pain, including 101 diabetic patients and 181 nondiabetic patients (mean age 63 ± 9.6 years), underwent coronary angiography and EBCT with determination of CCS using Agatston’s method. Luminal stenosis ≥50% was defined as significant coronary stenosis.

RESULTS — Angiography identified 205 patients with significant stenoses (89 of 101 diabetic patients, 114 of 181 nondiabetic patients). The sensitivity and specificity of EBCT to detect significant coronary stenosis were not significantly different between diabetic and nondiabetic patients. In diabetic patients, a CCS ≥90 was associated with 75% sensitivity and 75% specificity, whereas a CCS ≥200 was associated with 64% sensitivity and 83% specificity.

CONCLUSIONS — We demonstrated that calcification of the coronary arteries in symptomatic diabetic patients is well associated with severity of coronary stenosis, as in nondiabetic patients.

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Cardiovascular disease is the chief cause of morbidity and mortality in diabetic patients (1). Over half of all diabetic patients eventually die from a complication of cardiovascular disease. It has been reported that the 7-year cardiovascular mortality rate among patients with type 2 diabetes without a prior history of myocardial infarction is as high as that in nondiabetic patients with previous infarction (2). This implies that diabetic patients without known infarction may have advanced coronary atherosclerosis. Various screening tests are available to identify patients at high risk for atherosclerotic disease, including exercise electrocardiogram (ECG) testing, thallium myocardial scintigraphy, and stress echo coronary angiography. However, there is no consensus concerning the appropriate screening test for coronary disease in patients with diabetes. Exercise ECG testing has a relatively high specificity and sensitivity (68 and 77%, respectively) (3), but often diabetic patients cannot perform an exercise test because of complications such as artherosclerosis obliterans. Thallium scintigraphy also has satisfactory sensitivity and specificity but is expensive to perform.

Electron-beam computed tomography (EBCT) can noninvasively and accurately detect coronary calcification, which is a predictor of ischemic heart disease (3). Plaque calcifications usually precede luminal narrowing and the onset of angina symptoms. The sensitivity and specificity of EBCT for the detection of stenosis have been reported to be >90 and >50%, respectively (4). A 19-month follow-up study of 1,173 asymptomatic patients demonstrated that EBCT could accurately predict a cardiovascular event (5).

Medial calcification (Mönckeberg’s sclerosis) of the arteries of the lower extremities is typical for diabetic arteriosclerosis (6) and is an independent predictor of cardiovascular events in diabetic patients (7). Although several autopsy (8,9) and angiographic studies (10) have reported larger raised atherosclerotic lesions and more severe and diffuse coronary atherosclerosis in diabetic patients, the significance of coronary calcifications in diabetic patients has not yet been determined. Recently, several studies have reported the extent of coronary arteriosclerosis is as high as that in nondiabetic patients with previous infarction (2). This implies that diabetic patients without known infarction may have advanced coronary atherosclerosis. Various screening tests are available to identify patients at high risk for atherosclerotic disease, including exercise electrocardiogram (ECG) testing, thallium myocardial scintigraphy, and stress echo coronary angiography. However, there is no consensus concerning the appropriate screening test for coronary disease in patients with diabetes. Exercise ECG testing has a relatively high specificity and sensitivity (68 and 77%, respectively) (3), but often diabetic patients cannot perform an exercise test because of complications such as artherosclerosis obliterans. Thallium scintigraphy also has satisfactory sensitivity and specificity but is expensive to perform.

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Coronary calcium in diabetes

Table 1—Clinical characteristics of subjects

<table>
<thead>
<tr>
<th></th>
<th>Diabetic patients</th>
<th></th>
<th>Nondiabetic patients</th>
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<tbody>
<tr>
<td></td>
<td>With stenosis</td>
<td>Without stenosis</td>
<td>With stenosis</td>
<td>Without stenosis</td>
</tr>
<tr>
<td>n</td>
<td>89</td>
<td>12</td>
<td>114</td>
<td>67</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.4 ± 9.5</td>
<td>64.9 ± 4.8</td>
<td>62.9 ± 9.3</td>
<td>60.2 ± 10.5</td>
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<tr>
<td>Duration of diabetes</td>
<td>10.3 ± 9.6</td>
<td>13.3 ± 11.4</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Men/women</td>
<td>66/23</td>
<td>7/5</td>
<td>91/23</td>
<td>40/27</td>
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<tr>
<td>Medication (no/yes)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>30/59</td>
<td>5/7</td>
<td>63/51</td>
<td>26/41</td>
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<tr>
<td>Hyperlipidemia</td>
<td>65/24</td>
<td>6/6</td>
<td>29/85</td>
<td>16/51</td>
</tr>
<tr>
<td>Method for controlling diabetes (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>32</td>
<td>6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>α-glucosidase inhibitor</td>
<td>3</td>
<td>5</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Sulfonylurea</td>
<td>30</td>
<td>0</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Insulin</td>
<td>24</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.5 ± 3.6</td>
<td>25.3 ± 4.6</td>
<td>23.5 ± 3.3</td>
<td>23.8 ± 3.5</td>
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<td>Systolic blood pressure (mmHg)</td>
<td>137 ± 21</td>
<td>146 ± 22*</td>
<td>128 ± 25</td>
<td>134 ± 21</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75 ± 14</td>
<td>82 ± 19</td>
<td>75 ± 13</td>
<td>78 ± 13</td>
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<tr>
<td>Cholesterol (mg/dl)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Total (mg/dl)</td>
<td>194.9 ± 44.3</td>
<td>195.3 ± 45.6</td>
<td>192.2 ± 38.0</td>
<td>194.3 ± 37.7</td>
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<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>38.3 ± 10.6*</td>
<td>47.5 ± 21.6</td>
<td>42.7 ± 12.1</td>
<td>47.2 ± 14.1</td>
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<tr>
<td>Triglycerides (mg/dl)</td>
<td>158.1 ± 73.4</td>
<td>166.9 ± 92.1*</td>
<td>132.1 ± 78.1</td>
<td>138.4 ± 63.6</td>
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<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>125.0 ± 42.1</td>
<td>114.3 ± 47.6</td>
<td>123.1 ± 32.7</td>
<td>119.4 ± 31.5</td>
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<td>HbA1c (%)</td>
<td>7.07 ± 1.80†</td>
<td>6.75 ± 1.24†</td>
<td>5.21 ± 0.67</td>
<td>5.14 ± 0.58</td>
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<td>Smoking index</td>
<td>636 ± 725</td>
<td>109 ± 362</td>
<td>698 ± 633</td>
<td>405 ± 507</td>
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</tbody>
</table>

Data are means ± SD. Smoking index defined as cigarettes per day × number of years. *P < 0.05 vs. other three groups; †P < 0.05 between diabetic and nondiabetic patients in same category.

calcification in diabetic patients using EBCT. In type 1 diabetic patients, Olson et al. (11) reported that the coronary calcification score (CCS) had 100% sensitivity for a confirmed history of myocardial infarction or obstructive cardiovascular disease. In type 2 patients, Schurgin et al. (12) showed that asymptomatic diabetic patients had a significant increase in the prevalence of coronary calcification score compared with matched nondiabetic control groups. However, it is not known whether coronary calcifications in diabetic patients are associated with the presence of significant coronary stenoses. In this study, to examine the effect of diabetes on the association of EBCT-defined coronary calcification and atherosclerosis, we evaluated the relationship between coronary calcifications and angiographic stenosis in symptomatic patients with or without diabetes.

RESEARCH DESIGN AND METHODS — We evaluated 282 patients (204 men and 78 women), including 101 diabetic patients and 181 nondiabetic patients, who underwent elective coronary angiography and EBCT. This study included patients who, between March 1995 and August 1998, presented consecutively with chest pain suggestive of angina pectoris or with ambiguous symptoms but had resting ECG findings suggestive of myocardial ischemia. Informed consent was obtained from all patients before examination. An institutional review committee approved this study. Blood pressure was measured in the supine position using a sphygmomanometer. Clinical laboratory data were obtained in our institution, as previously reported (13). The clinical characteristics of the patients are summarized in Table 1. Of the 101 diabetic patients, 63 patients were taking medication for their diabetes (sulfonylureas, 30; α-glucosidase inhibitors, 8; and insulin, 25). Of the 42 patients not taking medication, 40 had no history of diabetes.

E elective coronary angiography was performed in multiple projections using standard techniques. The angiograms were reviewed by four experienced cardiologists who were unaware of the results of the EBCT study or the clinical data. Significant coronary artery stenosis was defined as ≥50% narrowing of the arterial lumen observed in multiple right anterior oblique and left anterior oblique views. Any stenosis of a main coronary artery (left main trunk [LMT], left anterior descending artery [LAD], left circumflex artery [LCx], and right coronary artery [RCA]) was graded as 50, 75, 90, or 99%. Nonobstructive disease was defined as a stenosis of 0–50%. The inter- and intra-observer variability of grading was 8 and 3%, respectively. The atherosclerosis (ATS) index was calculated by summing the percent narrowing for all stenosis, including multiple stenoses in the same main vessel (14).

The EBCT study was performed within 2 weeks before or after angiography with an Imatron C100 scanner, using a 100-ms exposure time (3). ECG triggering was set to 80% of the RR interval. In all, 20 consecutive 3-mm slices, beginning 1 cm below the carina and progressing caudally to include the proximal coronary arteries, were obtained. The CCS was calculated based on the area and density using Agatston's method (15) for each of the major coronary arteries: LMT, LAD, LCx, and RCA. The images were evaluated by four experienced observers, who had no knowledge of the clinical or angiographic data. Two contiguous pixels with an attenuation coefficient >130
Hounsfield units were defined as a calcium deposit. The interscan variability of the Agatston score was 11.5%. The intra-observer correlation was 0.99. The calcium score was transformed by taking the natural log of (1 + total coronary calcification score).

Differences in coronary calcification scores between two independent groups were analyzed by using the nonparametric Mann-Whitney U test, because the distribution of calcification scores was extremely asymmetric in some patient groups. One-way ANOVA, followed by Scheffe's tests, was performed for demographic and risk factors (except HbA1c) values among four groups, and two-way analysis was performed for HbA1c and HDL cholesterol values to see the interaction between gender and stenosis.

The sensitivity was calculated as true positive/(true positive and false negative). Specificity was calculated as true negative/(true negative and false positive). Negative predictive value was calculated as true negative/(true negative and false negative). Receiver operator characteristic (ROC) curve analysis was also performed. The false-positive rate (100 specificity) was plotted on the X-axis and the sensitivity was plotted on the Y-axis corresponding to each cutoff value of CCS. Statistical power was calculated as 1-β error. All data are presented as means ± SD. All statistical analyses were performed using StatView 5.0 (SAS Institute, Cary, NC).

RESULTS

Patient demographics

The clinical characteristics of patients with angina are summarized in Table 1. Systolic blood pressure and HDL-cholesterol, triglyceride, and HbA1c concentrations differed significantly between diabetic and nondiabetic patients. There were significant differences in HDL-cholesterol among men and women with and without stenoses (men: 40.0 ± 10.7 vs. 43.2 ± 11.6 mg/dl, respectively; women: 44.4 ± 12.5 vs. 56.3 ± 18.8, respectively; P = 0.018, by two-way ANOVA followed by Scheffe's test). Table 2 shows the summary of EBCT total calcium scores and calcium scores for the individual major coronary arteries. Calcium scores for the 282 patients were 0–6,812, with a median value of 123, 25th percentile value of 8, and 75th percentile value of 569. Diabetic patients had more pronounced calcification than the nondiabetic patients (median [interquartile range]: 374.5 [858] vs. 23 [118]; P < 0.05), and nondiabetic patients (285.5 [684] vs. 2 [60.5]; P < 0.05) (Fig. 1A) In contrast, no significant differences were observed in the calcification scores of patients with stenoses between diabetic and nondiabetic patients (median [interquartile range]: 374.5 [858] vs. 286 [684]; P = 0.19) (Fig. 1A).

Because coronary artery calcium accumulates exponentially in advanced lesions and in older patients, we plotted the log-transformed calcification score after adjusting for patient age (Fig. 1B and C). Patients with significant stenoses (median [interquartile range]: 31 [186], 220 [516], 254 [803], and 459 [798] in patients in their 40s, 50s, 60s, and 70s, respectively) had greater coronary artery calcification than patients without stenoses for all age groups (median [interquartile range]: 0 [3], 1 [40.5], 30 [107], and 28 [84] in patients in their 40s, 50s, 60s, and 70s, respectively) (Fig. 1B). Diabetic patients with significant coronary stenoses groups (median [interquartile range]: 28.5 [270], 404 [815], 301 [803], and 510 [1,001] in patients in their 40s, 50s, 60s, and 70s, respectively) had similar amounts of coronary calcification as nondiabetic patients with stenoses for all age group groups (median [interquartile range]: 54 [194], 146 [443], 254 [825], and 438 [461] for
patients in their 40s, 50s, 60s, and 70s, respectively) (Fig. 1).

The sum of all angiographically detectable stenoses (ATS score) was calculated for each patient (14). The total ATS score was related to the quartile calculation score (Fig. 2). The mean ATS scores for diabetic and nondiabetic patients for each quartile were 87.1 ± 11006.156 and 153 ± 11006.166 in the first quartile, 203 ± 259 and 304 ± 205 in the second quartile, 302 ± 210 and 415 ± 278 in the third quartile, and 449 ± 249 and 537 ± 260 in the fourth quartile, respectively. In all quartiles of CCSs, mean ATS scores tended to be higher in diabetic than nondiabetic sub-

**ROC curve analysis**

ROC curve analysis was used to establish the diagnostic relationship between the total CCS and the angiographic severity of coronary artery stenosis. An area under the ROC curve >0.5 identifies tests with increasingly greater diagnostic accuracy. The areas under the ROC curve for diabetic and nondiabetic patients were 0.852 and 0.806, respectively (Fig. 3). The all-curve areas were statistically greater than a curve area of 0.5, suggesting that CCSs accurately predicted the severity of coronary stenosis in diabetic as well as nondiabetic patients.

**Optimal sensitivity and specificity of the calcium score for detecting significant coronary stenoses**

The optimum calcium score corresponds to the value at which the sensitivity and specificity are maximal for a given degree of angiographic stenosis. It can be defined as the maximum value for the sum of sensitivity and specificity for all calcium scores. Figure 4 demonstrates the definition of the optimum calcium score by identifying the intersection of the sensitivity and specificity curves predicting ≥50% angiographic stenosis. The optimum EBCT calcification score of 90 was associated with a sensitivity of 75% and specificity of 75% in diabetic patients, and a calcification score of 82 was associated with a sensitivity of 70% and specificity of 71% in nondiabetic patients (Fig. 4). A calcification score of 82 had positive predictive value of 95.4 and 78.1% and negative predictive value of 26.5 and 57.9%.
in diabetic and nondiabetic patients, respectively. Because only 12% (12/99) of the diabetic patients had no evidence of stenosis in our study, the negative predictive value was low in symptomatic diabetic patients. These results suggest that the positive predictive power of the calcium score was similar in diabetic and nondiabetic patients. Statistical powers for diabetic and nondiabetic patients were 71 and 65%, respectively, when the cutoff value of CCS was set at 90.

**Risk factors for coronary stenosis**

The risk factors were determined only 1 month within the time of angiography. Therefore, it is possible that risk factors such as cholesterol levels or blood pressure do not truly reflect a patient’s risk factors during the development of coronary disease. To assess this potential bias, patients were asked to report the duration of risk factors. The average duration of diabetes was 10.3 ± 9.6 years for diabetic patients with significant stenosis, and 13.3 ± 11.4 years for diabetic patients without stenosis (P = 0.57). Patients with >1 year of hypertension, hyperlipidemia, or taking an antihypertension or antihyperlipidemia drug were evaluated as having risk factors. To assess the chronic effect of diabetes, hypertension, and hyperlipidemia, mean values for at least 1 year, if available, were evaluated.

**CONCLUSIONS** — Vascular calcification occurs at two anatomic sites: in the intima, where it is invariably associated with atherosclerosis, and in the tunica media. Medial calcification (Monckeberg’s sclerosis) occurs independently of atherosclerosis and is almost exclusively associated with vascular smooth muscle cells, in contrast to intimal calcification, which occurs in macrophage- and lipid-rich atherosclerotic lesion. Of particular importance is that diabetes is associated with medial calcification of the peripheral vessels, which raises the questions of whether the calcification observed in coronary vessels could be medial or not and whether coronary artery calcification in diabetic patients could be overestimated as compared with the severity of stenosis. A modest correlation has been observed between the degree of coronary stenosis and the extent of coronary calcification. One autopsy study showed that plaques in type 1 diabetic subjects had a similar calcium content as did plaques in nondiabetic subjects with atherosclerosis. We have now demonstrated, in clinical practice, that the calcification of coronary arteries in symptomatic diabetic patients is associated with the severity of coronary stenosis.

In nondiabetic individuals, EBCT has been shown to be a cost-effective approach to the diagnosis of obstructive coronary disease. We have now shown that EBCT can be useful in the detection of significant coronary lesions in diabetic as well as nondiabetic symptomatic patients. Rumberger et al. (4) reported that a coronary calcium score of 80 had a sensitivity of 84% and a specificity of 84%. These data are in keeping with our finding that a CCS of 90 was associated with a sensitivity of 75% and a specificity of 75% for the detection of significant stenoses in diabetic patients (Fig. 4).

In our study, the extent of angiographically detectable stenoses in diabetic patients was not different from those of nondiabetic patients, after adjusting for the CCS (Fig. 2). However, histologic examination of coronary arteries that appeared normal by coronary angiography has shown that angiography can underestimate the extent of coronary atherosclerosis. Specifically, only 6.8% of angiographically normal coronary artery segments were reported to be normal by intravascular ultrasound. In contrast, coronary angiography could
detect acute coronary thrombosis. In such cases, EBCT could underestimate the angiographic findings.

Furthermore, histologic comparison (22) demonstrated that on per-heart, per-artery, and per-segment bases, a significant relation exists between the calcified area and plaque area. Calcium does not localize exclusively to sites with severe coronary artery stenosis. Thus, calcification may reflect the extent of atherosclerotic lesions for individual hearts but not necessarily for individual arteries.

Practically, in patients with typical angina symptoms, we would proceed with coronary angiography independent of coronary calcification. However, in patients with ambiguous symptoms, we could proceed with a noninvasive study, such as thallium scintigraphy, if they had low coronary calcification score. In patients with no symptoms, we could proceed with thallium scintigraphy or even angiography if they had a very high coronary calcification score.

One limitation of this study was its generalizability to the general diabetic population because of the selection bias. This study was limited by the fact that we studied only symptomatic patients undergoing coronary angiography. Therefore, the cutoff value for the coronary calcification score for detecting coronary stenosis determined in this study may not be applicable to asymptomatic diabetic patients. Further studies of clinical outcomes of asymptomatic diabetic patients may clarify this issue.

The identification of presymptomatic high-risk individuals can provide the opportunity to institute appropriate preventive strategies. Because EBCT can be performed without the need for exercise testing, it can be used without any risk for the complications of exercise testing. In conclusion, EBCT may be used to predict ischemic heart disease in diabetic patients.

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References