Increased Prevalence of Significant Coronary Artery Calcification in Patients With Diabetes

SUNITA SCHURGIN, MD
STUART RICH, MD
THEODORE MAZZONE, MD

OBJECTIVE — Coronary artery disease is the major cause of morbidity and mortality in patients with diabetes. Detection of coronary artery disease before the first myocardial infarction and before anginal symptoms will allow for strategies designed to reduce the cardiovascular event rate in this group of patients. Electron beam–computed tomography (EBCT) is a noninvasive technology for evaluating the extent of coronary artery atherosclerosis that relies on the detection of coronary artery calcium (CAC). We used EBCT to detect significant coronary artery atherosclerosis in diabetic patients without symptoms of heart disease.

RESEARCH DESIGN AND METHODS — We used EBCT to evaluate calcium in the coronary arteries of 139 consecutive diabetic patients scanned over a 20-month period. The CAC scores in this group were compared with a randomly selected nondiabetic control group and a control group that was selected to match a number of established cardiovascular risk factors.

RESULTS — Patients with diabetes had a significant increase in the prevalence of CAC scores ≥400 (25.9%) compared with the randomly selected (7.2%) and matched (14.4%) nondiabetic control groups. Scores in this range have been reported to be highly predictive for abnormal stress myocardial perfusion tomography and subsequent coronary events.

CONCLUSIONS — Our results, therefore, indicate a substantial prevalence of significant coronary artery disease in an asymptomatic diabetic patient population compared with nondiabetic control subjects. They also suggest that EBCT may be a useful approach for selecting a group of diabetic subjects who would benefit most from additional evaluation for subclinical coronary artery disease.

Diabetes Care 24:335–338, 2001

Diabetes is a common disease with prevalence rates that are predicted to grow significantly over the next several decades (1–3). The major cause of morbidity and mortality in diabetic patients is macrovascular atherosclerosis, most commonly in the coronary arteries (1–3). Coronary artery disease also accounts for a large portion of economic resources used for the care of adult patients with diabetes. In addition to this increased predisposition to coronary artery disease, patients with diabetes also appear to have a worse prognosis after their first myocardial infarction. Increased mortality in diabetic patients after myocardial infarction has been noted over both short- and long-term follow-up and results from a number of causes, including increased rates of left ventricular failure, reinfarction, and sudden death (4). Given the above considerations, it would be desirable to detect significant atherosclerosis in the coronary arteries before the first myocardial infarction and even before the first symptoms of coronary artery disease. There is no general agreement, however, regarding the best way to screen asymptomatic diabetic patients for significant coronary artery disease. The issue regarding screening in diabetic patients is complicated further by observations suggesting that these patients have an increased rate of ischemic coronary events without typical anginal chest pain (5,6).

Over the past several years, a number of technologies have been developed to detect and measure atherosclerosis in the coronary artery tree. Electron beam–computed tomography (EBCT) is one such noninvasive technology. A number of studies evaluating the usefulness of EBCT as a screening tool in asymptomatic patients have been recently reported (7,8). However, these studies were conducted in predominantly nondiabetic patient populations. In this study, we analyzed coronary artery calcium (CAC) scores in 139 consecutive patients with diabetes undergoing EBCT at our institution between March 1997 and August 1998. We found that these patients demonstrated a significant increase in the prevalence of high CAC scores compared with nondiabetic control subjects.

RESEARCH DESIGN AND METHODS

— Subjects were identified from the cohort of patients who underwent EBCT between March 1997 and August 1998 at the Rush Heart Scan in Chicago, Illinois. Patients were given a prescan questionnaire and were selected and analyzed based on self-reported answers. Only asymptomatic patients were selected for study; specifically, subjects denied chest pain, shortness of breath, or any history of heart disease. From the prescan questionnaire, 139 patients were selected on the basis of self-reported diabetes (type 1 or 2). This group of diabetic patients was initially compared with a group of 139 nondiabetic subjects who were randomly selected from the group of subjects undergoing EBCT dur-

From the Department of Medicine, Rush Medical College, Chicago, Illinois.
Address correspondence and reprint requests to Dr. Theodore Mazzone, Rush Medical Center, 1653 W. Congress Pkwy., Chicago, IL 60612. E-mail: tmazzone@rush.edu.
Received for publication 16 August 2000 and accepted in revised form 30 October 2000.
Abbreviations: CAC, coronary artery calcium; EBCT, electron beam–computed tomography; LAD, left anterior descending; SPECT, stress myocardial perfusion tomography.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Comparison of CAC score distribution between diabetic and randomly selected nondiabetic subjects*

Total CAC score	Diabetic subjects	Nondiabetic subjects
<5	33.1	51.8
5–100	21.6	20.9
100–400	19.4	20.1
>400	25.9	7.2

Data are %. The score distribution between diabetic and nondiabetic groups is significantly different ($P <$ 0.0005).

ing the same period. Additional analysis and comparison were done using a cohort of 139 nondiabetic patients who were randomly selected from the nondiabetic patient database to be matched for established cardiovascular risk factors. The following self-reported cardiac risk factors were matched: sex, age, current smoking status, family history of premature (age <55 years) coronary artery disease, hypertension, and elevated blood cholesterol. Only subjects who completed the entire questionnaire were eligible for selection into the study. The protocol was approved by the Institutional Review Board at Rush-Presbyterian-St. Luke's Medical Center.

Measurement of coronary artery calcification scores

EBCT was performed using an Imatron C100 scanner (Imatron, South San Francisco, CA) as previously described (9). Briefly, two sets of 20 transverse 3-mm–thick slices were obtained in an axial fashion to image the entire heart. CAC was measured with a densitometric program available on the Imatron scanner. Areas of increased density overlying coronary arteries were evaluated. Lesions were scored with calcium defined as present if found in at least two contiguous pixels where the attenuation was ≥130 Houndsfield units. Scans were interpreted by an experienced reader who was blinded to the patient's clinical data. Comparisons were made between the diabetic and nondiabetic group using score thresholds and intervals indicated in the tables and figures. Patients with CAC scores <5 were arbitrarily designated as normal because this range represents a minimal amount of atherosclerosis that is associated with a low likelihood for significant coronary artery disease (10) and, moreover, because very low scores in this range may not be reproducible.

Statistical analysis

SPSS for Windows (version 8.0; SPSS, Chicago) was used for data management and statistical analysis. Because the scores had statistically non-normal distributions, nonparametric statistical methods were used to analyze the data. The Mann-Whitney *U* test was done to compare the diabetic patients and the randomly selected nondiabetic control group with respect to score distribution. When diabetic patients were compared with the matched nondiabetic group, statistical methods were used that took into account the nonindependent structure of the data. A sign test was used to compare the diabetic and nondiabetic matched groups with respect to score distribution, and the McNemar test was used to compare these groups with respect to nominal percentages. A significance level of $P < 0.05$ was used for all statistical tests. No one-sided statistical tests were done.

RESULTS — In Table 1, the distribution of total CAC scores was compared between 139 diabetic subjects and 139 randomly selected control subjects. For the randomly selected nondiabetic group, the average age was 54 years, and there were 39 women and 100 men. In the diabetic group, the average age was 58 years, and there were 44 women and 95 men. The CAC scores (means ± SEM) for the diabetic subjects and random control group were 344 ± 58 and 103 ± 19, respectively. Because CAC score distribution was skewed, comparisons were made using the intervals indicated in Table 1. Comparing the two groups, no difference was detected for mid-range scores, but significantly more nondiabetic subjects had CAC scores <5 (51.8%) compared with diabetic subjects (33.1%). In the nondiabetic group, there were 64 patients with a score of 0, compared with 34 patients with this score in the diabetic group. Conversely, more diabetic subjects had scores ≥400 (25.9%) compared with the nondiabetic group (7.2%). The difference in score distribution between diabetic and nondiabetic subjects was significant ($P < 0.0005$).

Diabetes is associated with a number of well-established cardiovascular risk factors (1–3). We next compared CAC scores in the diabetic group with those in a nondiabetic group that was matched for age, sex, hypertension, smoking, family history of coronary artery disease, and elevated cholesterol. In the latter category, patients were separated into three groups: those reporting normal cholesterol levels, those who reported elevated cholesterol levels but were not on medication, and those who reported elevated cholesterol levels and were on specific cholesterol-lowering medication. The characteristics of the diabetic group and the matched control group are shown in Table 2; as can be seen, the group

Table 2—*Risk factor profile for the diabetic and matched nondiabetic groups*

Risk factor	Diabetic subjects	Nondiabetic subjects
n	139	139
Age (years)	58 (NA)	58 (NA)
Sex		
Female	44 (31.7)	44 (31.7)
Male	95 (68.3)	95 (68.3)
Hypertension		
Yes	71 (51.1)	71 (51.1)
No	68 (48.9)	68 (48.9)
Smoker		
Yes	8 (5.8)	8 (5.8)
No	131 (94.2)	131 (94.2)
Family history		
Yes	75 (54)	75 (54)
No	64 (46)	64 (46)
Cholesterol level		
Normal	67 (48.2)	67 (48.2)
High	41 (29.5)	41 (29.5)
High (on medication)	31 (22.3)	31 (22.3)

Data are *n* (%). NA, not applicable.

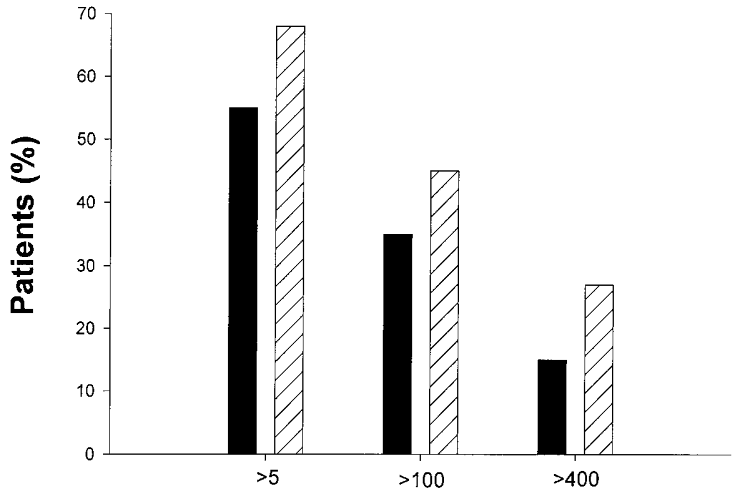

Figure 1—*The distribution of CAC scores in diabetic patients compared with matched nondiabetic subjects. The total CAC score is shown on the horizontal axis.* P *values between control and diabetic subjects for CAC scores >5, >100, and >400 are 0.058, 0.081, and 0.004, respectively. ■, Control subjects; ▨, diabetic subjects.*

selected from the nondiabetic patient database was identical for all of the identified cardiac risk factors. In the diabetic group, the CAC score was 344 ± 58 (as noted above), compared with 242 ± 47 for the matched nondiabetic group. As noted above, 34 diabetic patients had a score of 0. In the matched nondiabetic group, 47 patients had this score. Because score distribution was again skewed in both groups, statistical methods were applied to allow comparison of score distribution between the two groups. The data regarding total CAC score distribution between these two groups is provided in Fig. 1. Selection of a control group with cardiac risk factors to match those found in the diabetic group resulted in a prevalence of CAC scores ≥400 in 14.39% of the nondiabetic subjects. This is approximately double the rate detected in the randomly selected nondiabetic control subjects. However, this prevalence rate is still significantly lower than that found in the diabetic subjects (25.9%). The prevalence of moderately increased CAC scores (between 100 and 400) is similar in the diabetic and matched nondiabetic cohorts. This comparison can be made by subtracting the percentage of patients in each group with a total score ≥400 from the percentage with a total score ≥100. This calculation reveals a prevalence rate of ~20% in both the diabetic and the matched nondiabetic groups for CAC scores between 100 and 400. We also evaluated the topography of calcium distribution for any patient with a score >5 in the diabetic and matched nondiabetic groups (Table 3). As shown, diabetic patients had calcium present significantly more often in the left anterior descending (LAD) and circumflex arteries. This result is in agreement with a recently published detailed topographic analysis of calcium distribution showing that more advanced atherosclerosis is reflected by the increased frequency of calcium in the proximal LAD and proximal left circumflex arteries (10).

CONCLUSIONS — The detection of subclinical coronary artery disease in diabetic patients is gaining importance as diabetes is becoming more common, and additional information and tools to modify the risk of death from coronary artery disease are becoming available. The usefulness of EBCT in the diabetic patient population remains inadequately explored. Preliminary information has been reported in abstract form from a group of 135 patients with type 1 diabetes (11). Score intervals were not published for this group, but these patients had a higher prevalence of CAC compared with an unmatched asymptomatic nondiabetic group. The prevalence of CAC in the diabetic patient group was correlated with duration of diabetes, age, and hypertension. Two additional reports have recently appeared that included diabetic patient populations; however, scores and detailed analyses were not reported separately for diabetic patients (7,8). One study evaluated the results of stress myocardial perfusion tomography (SPECT) after EBCT (7). In this analysis, no subjects with a CAC score <10 had abnormal SPECT, whereas 46% of those with scores ≥400 had abnormal SPECT. By logistic regression, the total CAC score was the best single predictor for an abnormal SPECT exam; however, the presence of diabetes was also a significant predictor by univariate analysis. As noted above, scores were not reported separately for patients with diabetes; therefore, a high rate of significantly elevated scores may have accounted for the latter association. In a subsequent study, the total CAC score was found to be significantly correlated with the development of acute myocardial infarction or cardiac death during 32 ± 7 months of follow-up (8). In this group of patients, 4.8% of those with CAC scores ≥400 had an event during the follow-up, whereas only 1% of those with CAC scores between 1 and 99 experienced an adverse event. In this group of patients, only 7% of all subjects had a CAC score ≥400.

For the current study, we analyzed all diabetic patients screened over a 20-month period and compared CAC scores to randomly selected and matched nondiabetic control groups. The most significant finding of our study is the high prevalence of CAC scores ≥400 in patients with diabetes: 26 vs. 7.2% in the randomly selected nondiabetic group. This latter percentage is similar to the prevalence of scores ≥400 reported in large groups of asymptomatic patients, as noted above (8). After acquisition of a control group matched for multiple cardiac risk

Table 3—***Diabetic and matched nondiabetic patients with calcium detected in specific coronary arteries***

	Diabetic subjects	Nondiabetic subjects	*P*
Left main	10.1	14.4	0.345
Right coronary	40.3	37.4	0.078
Circumflex	37.4	25.2	0.027
LAD	61.9	49.6	0.027

Data are %.

factors, the prevalence of scores ≥400 increased to 14% in the nondiabetic patient group. However, prevalence of CAC scores ≥400 was still significantly higher in the diabetic patient cohort.

Several important implications of our findings can be considered. First, for asymptomatic patients with diabetes, EBCT may be a useful screening test for selecting those who would benefit most from additional testing (e.g., patients with scores ≥400). As noted above, almost 50% of patients with CAC scores ≥400 will have positive SPECT (7). Based on our results, >25% of unselected asymptomatic diabetic patients will have CAC scores ≥400, almost fourfold higher than the prevalence of such scores in nondiabetic unselected asymptomatic patients. Second, in our analysis, even after matching cardiovascular risk factors including sex, hypertension, smoking status, family history, and cholesterol level, patients with diabetes had CAC scores ≥400 almost twice as frequently as nondiabetic patients. This confirms the observation frequently reported in the literature that patients with diabetes have more advanced coronary artery disease than nondiabetic patients, even after controlling for multiple cardiovascular risk factors (1–3). Third, based on published results, patients with CAC scores ≥400 will have a significant rate of coronary events over the next 3- to 4-year period (8). The results of our study, therefore, indicate that EBCT may be useful for identifying a high-risk group of diabetic patients to more effectively and rapidly evaluate intervention strategies to reduce coronary events in this population.

There are two issues that will require clarification in the future. First, because the average age of our diabetic subjects was 58 years, it is likely they were overwhelmingly patients with type 2 diabetes. However, some patients with type 1 diabetes may have been included, and potential differences in CAC scores between these two patient populations were not addressed in our study. Second, our analysis was based on patient answers on a prescan questionnaire. Self-reporting of cardiac risk factors may underestimate true prevalence (12,13). Whereas it is not possible to rule out systematic differences in self-reporting behavior as factors affecting our results, randomly distributed reporting errors would tend to minimize associations, meaning our analysis may have actually underestimated the strength of the association between diabetes and the prevalence of CAC.

In summary, information in the literature indicates that whereas the presence of significant coronary artery calcification predicts subsequent cardiac events, most events may not occur in patients with significant CAC because of the low prevalence rate for high scores in unselected patients (14,15). Specifically, scores ≥400, which are highly correlated with subsequent positive SPECT and subsequent cardiac events, only occur in <10% of asymptomatic nondiabetic patients. Our results, however, indicate that CAC scores ≥400 occur in >25% of asymptomatic diabetic patients. As noted above, silent ischemia may be more common in diabetic patients (5,6), thereby increasing the need for detection of significant coronary artery disease in asymptomatic patients. Further studies are needed to identify the most cost-effective way of managing asymptomatic coronary artery disease in this patient population. However, the identification of high-risk patients may help select those patients who would benefit most from additional testing (e.g., noninvasive stress imaging). In addition, identification of significant CAC could help reinforce patient compliance and identify patients who may benefit from intensification of medical therapy, such as the addition of ACE inhibitors. These issues underscore the need for further evaluation of EBCT technology to maximize potential benefit in terms of identifying disease and instituting intensive intervention therapy for this high-risk patient population.

Acknowledgments — The authors thank Susan Shott, PhD, for assistance with statistical analysis and Stephanie Thompson for assistance with preparation of the manuscript.

References

1. Mazzone T: Current concepts and controversies in the pathogenesis, prevention, and treatment of the macrovascular complications of diabetes. *J Lab Clin Med* 135:437–443, 2000
2. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC, Sowers JR: Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 100:1134–1146, 1999
3. American Diabetes Association; the National Heart, Lung, and Blood Institute; the Juvenile Diabetes Foundation International; the National Institute of Diabetes and Digestive and Kidney Diseases; and the American Heart Association: Diabetes mellitus: a major risk factor for cardiovascular disease (Editorial). *Circulation* 100: 1132–1133, 1999
4. Aronson D, Rayfield EJ, Chesebro JH: Mechanisms determining course and outcome of diabetic patients who have had acute myocardial infarction. *Ann Intern Med* 126:296–306, 1997
5. Chiariello M, Indolfi C: Silent myocardial ischemia in patients with diabetes mellitus. *Circulation* 93:2089–2091, 1996
6. Janand-Delenne B, Savin B, Habib G, Bory M, Vague P, Lassmann-Vague V: Silent myocardial ischemia in patients with diabetes: who to screen. *Diabetes Care* 22: 1396–1400, 1999
7. He ZX, Hedrick TD, Pratt CM, Verani MS, Aquino V, Roberts R, Mahmarian JJ: Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischemia. *Circulation* 101: 244–251, 2000
8. Raggi P, Callister TQ, Cooil B, He ZX, Lippolis NJ, Russo DJ, Zelinger A, Mahmarian JJ: Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 101:850–855, 2000
9. McLaughlin VV, Balogh T, Rich S: Utility of electron beam computed tomography to stratify patients presenting to the emergency room with chest pain. *Am J Cardiol* 84:327–328, 1999
10. Schmermund A, Mohlenkamp S, Baumgart D, Kriener P, Pump H, Gronemeyer D, Seibel R, Erbel R: Usefulness of topography of coronary calcium by electron-beam computed tomography in predicting the natural history of coronary atherosclerosis. *Am J Cardiol* 86:127–132, 2000
11. Rewers M, Ehrlich J, Jensen L, Seigel R, Barriga K, Garg S, Janowitz W, Eckel RH: High prevalence of asymptomatic coronary atherosclerosis detected by electron beam computed tomography in young adults with IDDM (Abstract). *Diabetes* 47:A12, 1998
12. Psaty BM, Kuller LH, Bild D, Burke GL, Kittner SJ, Mittelmark M, Price TR, Rautaharju PM, Robbins J: Methods of assessing prevalent cardiovascular disease in the cardiovascular health study. *Ann Epidemiol* 5: 270–277, 1995
13. Mittelmark MB, Psaty BM, Rautaharju PM, Fried LP, Borhani NO, Tracy RP, Gardin JM, O'Leary DH: Prevalence of cardiovascular diseases among older adults: the cardiovascular health study. *Am J Epidemiol* 137:311–317, 1993
14. Secci A, Wong N, Tang W, Wang S, Doherty T, Detrano R: Electron beam computed tomographic coronary calcium as a predictor of coronary events: comparison of two protocols. *Circulation* 96:1122–1129, 1997
15. Wong ND, Detrano RC, Abrahamson D, Tobis JM, Gardin JM: Coronary artery screening by electron beam computed tomography: facts, controversy, and future. *Circulation* 92:632–636, 1995