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The Prevalence of Coronary Artery Calcium Among Diabetic Individuals Without Known Coronary Artery Disease

Julie Anne Hoff, PhD, RN,*† Lauretta Quinn, PhD, RN,† Alexander Sevrukov, MD,*
Rebecca B. Lipton, PhD, MPH, BSN,‡ Martha Daviglus, MD, PhD,§ Daniel B. Garside, MS,§
Niraj K. Ajmere, BS,* Sanjay Gandhi, MD,* George T. Kondos, MD*
Chicago, Illinois

OBJECTIVES We sought to examine the age and gender distribution of coronary artery calcium (CAC) by diabetes status in a large cohort of asymptomatic individuals.

BACKGROUND Among individuals with diabetes, coronary artery disease (CAD) is a major cause of morbidity and mortality. Electron-beam tomography (EBT) quantifies CAC, a marker for atherosclerosis.

METHODS Screening for CAC by EBT was performed in 30,904 asymptomatic individuals stratified by their self-reported diabetes status, gender, and age. The distribution of CAC across the strata and the association between diabetes and CAC were examined.

RESULTS Compared with nondiabetic individuals (n = 29,829), those with diabetes (n = 1,075) had higher median CAC scores across all but two age groups (women 40 to 44 years old and men and women ≥70 years old). Overall, the likelihood of having a CAC score in the highest age/gender quartile was 70% greater for diabetic individuals than for their nondiabetic counterparts.

CONCLUSIONS Younger diabetic individuals appear to have calcified plaque burden comparable to that of older individuals without diabetes. These findings call for future research to determine if EBT-CAC screening has an incremental value over the current CAD risk assesment of individuals with diabetes. (J Am Coll Cardiol 2003;41:1008–12) © 2003 by the American College of Cardiology Foundation

Approximately 10.3 million Americans have physician-diagnosed diabetes, whereas an estimated 5.4 million people are undiagnosed (1). Cardiovascular complications are the major cause of diabetes-associated morbidity and mortality, as two-thirds of people with diabetes die of heart or blood vessel disease (2–4).

Routine assessment of conventional risk factors accounts for only a portion of the increased coronary artery disease (CAD) risk observed among diabetic individuals (5). Electron-beam tomography (EBT) is a noninvasive tool for the detection and quantification of coronary artery calcium (CAC), a marker for atherosclerosis. The extent of CAC strongly correlates with the overall magnitude of atherosclerotic plaque burden (6) and with the development of subsequent coronary events (7,8). Previously published reports have demonstrated, in limited samples of diabetic individuals, greater calcified plaque burden by EBT, as compared with nondiabetic individuals (9–12). The present study supplements the existing reports of the association between EBT-CAC and diabetes by examining the age and gender distribution of CAC in a large cohort of asymptomatic diabetic and nondiabetic individuals.

METHODS

Study sample. Between 1993 and 1999, 32,477 individuals (30 to 90 years old) were self-referred for EBT CAC screening. Before screening, subjects completed a questionnaire eliciting demographic and CAD risk factor information. Of these individuals, 1,573 were excluded from this analysis because of a history of clinical CAD. The University of Illinois at Chicago (UIC) Internal Review Board approved the study protocol.

Self-reported CAD risk factors included a history of smoking, diabetes, hypercholesterolemia, hypertension, and a family history of CAD. The definitions of self-reported CAD risk factors have been reported previously (13). The validity of self-reported histories of hypercholesterolemia, diabetes, and hypertension was examined in a peripheral study (14). The kappa coefficients for hypercholesterolemia, diabetes, and hypertension were 0.796 ($p < 0.001$), 0.783 ($p < 0.001$), and 0.36 ($p < 0.01$), respectively. The incongruity observed for hypertension was mainly due to an abundance of individuals previously diagnosed with hypertension whose high blood pressure was controlled with

From the *Department of Medicine, Section of Cardiology, University of Illinois College of Medicine, Chicago; †Department of Medical Surgical Nursing, University of Illinois College of Nursing, Chicago; ‡Division of Pediatric Endocrinology, University of Chicago, Chicago; and§Department of Preventive Medicine, Northwestern University School of Medicine, Chicago, Illinois. This research was supported with internal funding from the University of Illinois at Chicago, Department of Medicine, Section of Cardiology.

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Abbreviations and Acronyms

ARIC	= atherosclerosis Risk in Communities Study
CAC	= coronary artery calcium
CAD	= coronary artery disease
EBT	= electron-beam tomography
NHANES	= National Health And Nutrition Education Survey
UIC	= University of Illinois at Chicago

life-style modification and who presented with normal blood pressure at the time of examination.

Electron-beam tomography. The EBT-CAC scans were obtained using a C-100 or C-150 scanner (GE Imatron, South San Francisco, California). Using electrocardiographic triggering at 60% to 80% of the ECG RR interval, two sets of 100-ms/3-mm images (40 and 20 slices) were acquired. The CAC score was calculated using the Agatston method (15). The details of the UIC scanning protocol have been published elsewhere (13).

Data analysis. The study sample was stratified by gender and into eight exclusive five-year age groups (from <40 to ≥70 years old). Analysis was conducted using SPSS version 10.0 for Windows (SPSS, Inc., Chicago, Illinois). The Mann-Whitney *U* test was used to compare median CAC scores between diabetic and nondiabetic individuals by age group. Chi-square analysis was used to compare the prevalence of risk factors and CAC. Controlling for age and body mass index, a multivariable logistic regression analysis was used to examine the association between CAD risk factors and CAC scores ≥75th percentile for age/gender (13).

RESULTS

Sample characteristics. The study sample consisted of 22,188 men and 8,716 women (30 to 90 years old). Diabetes was reported by 747 of the men (3.4%) and 328 of the women (3.8%). Demographics, risk factors, and CAC characteristics for the study sample stratified by gender and diabetes status are summarized in Table 1. Generally, diabetic individuals were older and had a greater prevalence of hypertension, cigarette use, and CAC, as compared with those without diabetes. Overall, the mean (±SD) total CAC score in the diabetic group was 284 ± 684, as compared with 106 ± 328 in those without diabetes. The reported socioeconomic indicators (income and education) for both the diabetic and nondiabetic individuals were higher than the national averages. Despite the high socioeconomic status of the study sample, the under-representation of women and minorities, and the use of self-referred individuals, the prevalence figures for CAD risk factors in the present study sample were similar to

Table 1. Demographics, Risk Factors, and CAC Characteristics of Men and Women With and Without Diabetes

Men	Diabetes (n = 747)	No Diabetes (n = 21,441)	p Value
Mean age (yrs)	55 ± 9	50 ± 9	< 0.001
Annual income >$50,000	82	74	0.001
Education >12 years	94	97	0.002
Family history of CAD	52	52	0.84
Past or current smoking	62	51	< 0.001
Hypertension	47	20	< 0.001
Hypercholesterolemia	37	36	0.68
Mean body mass index (kg/m^2)	30 ± 5	28 ± 4	< 0.001
Presence of CAC (>0)	90	77	< 0.001
Mean CAC score	346 ± 749	127 ± 359	< 0.001
Median CAC score (interquartile range)	63 (5–365)	6 (1–80)	< 0.001
Total CAC ≥75% age/gender percentile	39	24	< 0.001
Women	**Diabetes (n = 328)**	**No Diabetes (n = 8,388)**	**p Value**
Mean age (yrs)	56 ± 10	54 ± 9	< 0.001
Annual income >$50,000	56	67	< 0.001
Education >12 years	85	95	< 0.001
Family history of CAD	57	56	0.73
Past or current smoking	49	47	0.52
Hypertension	55	22	< 0.001
Hypercholesterolemia	36	39	0.26
Mean body mass index (kg/m^2)	31 ± 6	27 ± 5	< 0.001
Presence of CAC (>0)	75	53	< 0.001
Mean CAC score	142 ± 479	52 ± 219	< 0.001
Median CAC score (interquartile range)	5 (0–104)	1 (0–11)	< 0.001
Total CAC ≥75% age/gender percentile	40	23	< 0.001

Differences between diabetic and nondiabetic individuals were examined using the Pearson's chi-square test (for percentages), independent samples *t* test (for age, body mass index, and mean CAC score), and Mann-Whitney *U* test (for median CAC score). Data are presented as the mean value ± SD or percentage of subjects.

CAC = coronary artery calcium; CAD = coronary artery disease.

Table 2. Median CAC Scores of Men and Women With and Without Diabetes

	Diabetes		No Diabetes		
Men	n	Median CAC Score	n	Median CAC Score	p Value
Age group (years)					
<40	46	4	3,005	1	< 0.001
40–44	63	13	3,653	1	< 0.001
45–49	100	9.5	4,322	3	0.001
50–54	144	42	4,142	14	< 0.001
55–59	160	111	2,912	43	< 0.001
60–64	117	192	1,860	105	< 0.001
65–69	72	378	955	152	< 0.001
≥70	45	343	592	301	0.77
Total	747	63	21,441	6	< 0.001

	Diabetes		No Diabetes		
Women	n	Median CAC Score	n	Median CAC Score	p Value
Age group (years)					
<40	21	1	514	0	< 0.001
40–44	32	0	846	0	0.14
45–49	32	1	1,398	0	0.01
50–54	74	8.5	1,826	0	< 0.001
55–59	52	7.5	1,522	1	< 0.001
60–64	47	21	1,105	2	0.003
65–69	34	104	712	5	0.006
≥70	36	114	465	52	0.54
Total	328	5	8,388	1	< 0.001

The Mann-Whitney *U* test was used to compare coronary artery calcium (CAC) scores between diabetic and nondiabetic subjects within each five-year age group. The analyses were performed separately for men and women.

estimates for the general U.S. population, using data from the National Health And Nutrition Education Survey (NHANES) and the Atherosclerosis Risk in Communities (ARIC) study (16,17). Table 2 provides pairwise comparisons of median CAC scores by gender, age, and diabetes status. Compared with nondiabetic subjects, men and women with diabetes exhibited higher CAC scores across all ages, with the exception of women 40 to 44 years of age and men and women ≥70 years of age. Within each five-year age group, diabetic men exhibited consistently higher CAC scores than did diabetic women ($p < 0.001$ for all comparisons), except for the youngest age group (subjects <40 years old; $p = 0.05$). Table 3 provides the results of a logistic regression analysis examining the association between CAD risk factors and a total CAC score in the highest age/gender quartile. For both genders, every CAD risk factor was significantly associated with a total CAC score in the highest age/gender quartile. Diabetes was the strongest predictor for having a CAC score in the highest quartile for both genders. Overall, the likelihood of having a CAC score in the highest age/gender quartile was 70% greater for diabetic individuals than for their nondiabetic counterparts.

Among men and women, an association between age and the extent of CAC has been demonstrated previously (13). As diabetic individuals were significantly older than their nondiabetic counterparts, the age-adjusted multivariable logistic regression analysis described previously was repeated

Table 3. Association Between CAD Risk Factors and the Highest Age and Gender Quartile of Coronary Artery Calcium Score (≥ 75%) Among Men and Women (n = 30,904)

	Men		Women	
	Odds Ratio	p Value	Odds Ratio	p Value
Age (yrs)	1.001 (0.99–1.004)	0.77	0.998 (0.992–1.003)	0.41
Body mass index (kg/m^2)	1.04 (1.03–1.05)	< 0.001	1.05 (1.04–1.06)	< 0.001
Family history of CAD (yes/no)	1.19 (1.11–1.27)	< 0.001	1.16 (1.04–1.29)	0.01
Hypercholesterolemia (yes/no)	1.23 (1.15–1.32)	< 0.001	1.39 (1.24–1.55)	< 0.001
Cigarette use (yes/no)	1.36 (1.27–1.45)	< 0.001	1.57 (1.41–1.75)	< 0.001
Hypertension (yes/no)	1.41 (1.31–1.53)	< 0.001	1.51 (1.33–1.71)	< 0.001
Diabetes (yes/no)	1.73 (1.47–2.03)	< 0.001	1.69 (1.32–2.16)	< 0.001

The logistic regression model was constructed using block entry of all predictor variables. The analyses were performed separately for men and women.

CAD = coronary artery disease.

using a 3-to-1 age/gender frequency-matched sample of 3,225 randomly selected nondiabetic control subjects. In this model, the associations between CAD risk factors and a total CAC score ≥75th percentile for age/gender were very similar to those reported for the unmatched sample, with the exception of cigarette use and hypercholesterolemia in men in whom the magnitude of risk was similar but the significance at the 0.05 level was lost.

DISCUSSION

Electron-beam tomography is gaining acceptance as a tool for the detection of subclinical CAD and for guiding diagnostic and treatment strategies (18). This study reports the distribution of CAC in a large sample of diabetic men and women without known CAD. Our findings demonstrate that asymptomatic diabetic men and women have higher median CAC scores than do their nondiabetic counterparts, with a few exceptions. For women 40 to 44 years of age and men and women ≥70 years of age, the most probable explanation for the lack of a difference in EBT-CAC median scores by diabetes status is a lack of power resulting from the small number of individuals in each group. It is also possible that the older diabetic individuals in this study were long-term, well-controlled survivors or possibly newly diagnosed with diabetes. Another finding was that among subjects with diabetes at any given age, men exhibited significantly greater calcified plaque burden, as compared with women.

Among the CAD risk factors examined, diabetes was the strongest correlate for a CAC score in the highest age-specific quartile for both genders, even when using an age/gender-matched sample of nondiabetic control subjects.

The use of EBT for the detection of CAD in diabetic individuals has been studied previously. In a recent study, Schurgin et al. (9) examined the degree of CAC in a sample of 139 asymptomatic diabetic individuals, as compared with the randomly selected nondiabetic group. Among diabetic subjects, 26% had scores ≥400, compared with 7.2% in the randomly selected nondiabetic group. Another group of researchers (Olson et al. [10]) found that CAC had 84% sensitivity for clinical CAD in type I diabetic men and 71% sensitivity in type I diabetic women. Khaleeli et al. (11) determined that 168 symptomatic (anginal) diabetic individuals had a higher prevalence of CAC, as compared with 155 asymptomatic diabetic individuals. Interestingly, no significant difference was determined between diabetic men and women with regard to CAC scores at any given age. The failure to show a significant difference, however, could be attributable to the small sample size ($n = 323$) and the small correlation coefficients ($r = 0.28$ for men and $r = 0.36$ for women) reported.

There are some limitations of the present study, which will be addressed in future research. The CAD risk factors were assessed using self-reporting, with no clinical measurement. Yet, in a peripheral study, we found high levels of agreement between self-reported and clinically measured diabetes status (14). In addition, all study subjects were self-referred, and there is a concern that self-referred individuals may represent extremes of the population relative to health status. In considering these limitations, it is important to note that the prevalence rates for CAD risk factors in the study sample were comparable to those reported in two population-based studies (16,17). Also, one-third of type II diabetes is undiagnosed (19). It is quite possible that there were individuals with impaired glucose tolerance or type II diabetes who were categorized as nondiabetic. In light of this limitation, the observed differences by diabetes status would be attenuated, and therefore it is possible that the differences between diabetic and nondiabetic individuals are greater than we report.

The clinical utility of noninvasive evaluation of atherosclerosis in asymptomatic diabetic individuals remains unclear. Because diabetes places individuals in the same risk category as individuals with known CAD (2), noninvasive testing such as EBT-CAC screening would do little to change the current clinical management of traditional cardiovascular risk factors. Yet future studies to determine whether CAC scores predict future clinical events in asymptomatic individuals with diabetes will help delineate a role for EBT in the clinical management of diabetes (20).

The increasing use of imaging modalities in population-based studies and clinical practice may enhance the utility of CAC screening, which could be an important tool in describing the natural history of coronary atherosclerosis in both impaired glucose tolerance and diabetes. Among prediabetic individuals, especially those with the metabolic syndrome, CAC screening could be particularly useful in the stratification of certain individuals into more aggressive risk factor management regimens. In addition, EBT-CAC screening results may potentially motivate individuals in their CAD risk reduction efforts. Further studies are needed to address these potential uses of CAC screening.

Reprint requests and correspondence: Dr. Julie Anne Hoff, DOM, Cardiology, 840 S. Wood Street (m/c 715), Chicago, Illinois 60612. E-mail: jahoff@uic.edu.

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