Reduced Coronary Artery and Abdominal Aortic Calcification in Hispanics With Type 2 Diabetes

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OBJECTIVE — To compare lifestyle factors, cardiovascular risk factors, and coronary artery calcium (CAC) and abdominal aortic calcium (AAC) levels in Hispanic and non-Hispanic white (NHW) individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS — We recently demonstrated in a small group of nonreferred, healthy, nondiabetic subjects that CAC was reduced in Hispanics compared with NHWs, despite a worse cardiovascular risk factor profile. In this study, we evaluated whether this ethnic disparity in vascular calcification was present in individuals with type 2 diabetes and in several different arterial beds. Hispanic and NHW subjects ($n = 245$) with type 2 diabetes were evaluated for cardiovascular risk factors using questionnaires and assays of plasma biomarkers. CAC and AAC were measured by electron-beam computer-assisted tomography.

RESULTS — Although Hispanics were slightly younger than NHWs, other standard risk factors and novel cardiovascular risk factors, including plasminogen activator-1 and fibrinogen levels, were similar between the groups. Despite the similar risk factor profile, the prevalence of cardiovascular disease (CVD) and mean and median levels of CAC and AAC were lower in Hispanics. Furthermore, the distribution of these calcium scores differed from that of NHWs ($P < 0.05$), with significantly fewer Hispanic subjects having high CAC or AAC scores. These differences were not explained by differences in CVD prevalence or any measured lifestyle or risk factor.

CONCLUSIONS — Hispanics with type 2 diabetes have reduced CAC and AAC levels compared with NHW subjects, suggesting a reduction in the overall burden of vascular calcification and atherosclerosis. These data are consistent with the notion that Hispanics are protected against the development of CVD.

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Numerous studies over the past several decades, using vital statistics data, have demonstrated reduced rates of total and cardiovascular mortality in Hispanics (1–4). Interestingly, epidemiological studies of cardiovascular risk factors have suggested that Hispanics are frequently more obese and insulin resistant compared with non-Hispanic whites (NHWs) and often, as a result, have higher triglyceride levels and lower HDL cholesterol levels (5–13). This apparent decreased rate of cardiovascular disease (CVD) in Hispanics, despite evidence of increased levels of several traditional and nontraditional risk factors, has been described as the "Hispanic paradox" (14,15). However, in several recent longitudinal cohort studies, rates of CVD have appeared equal or possibly greater in Hispanics compared with their NHW counterparts (16–20). It is important to note that in several of these studies, the comparison between ethnic groups may have been complicated by the greater prevalence and incidence of diabetes in the Hispanic population, which may greatly enhance the overall cardiovascular risk of this ethnic group in comparison with groups having reduced rates of diabetes.

To further assess this potential ethnic disparity in the propensity to develop CVD, investigators have tried to more directly measure the extent of underlying atherosclerosis in Hispanic and NHW populations. However, until recently, studies have not directly assessed coronary or aortic atherosclerosis in ethnic groups. The use of ultrafast electron-beam computed tomography (EBCT) scans to measure vascular calcium has now made this possible. Calcification of the coronary artery intima (CAC) is closely associated with atherosclerosis (21) and appears to be an important predictor of future CVD events (22–27). In one published study of CAC performed in Hispanics and NHWs who were referred for suspicion of CVD, coronary angiography was performed. The reduced extent of coronary calcification in Hispanics appeared to mirror the extent of obstructive lesions present in these same individuals (28). We recently demonstrated in a small group of healthy age-matched subjects who were free of known CVD that CAC was reduced in Hispanics compared with NHWs (29). We now assess whether this ethnic difference in vascular calcification

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Abbreviations: AAC, abdominal aortic calcium; CAC, coronary artery calcium; CVD, cardiovascular disease; EBCT, electron-beam computed tomography; MI, myocardial infarction; NHW, non-Hispanic white; PAI-1, plasminogen-activating factor 1; PVD, peripheral vascular disease; VA, Veterans Affairs.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

exists across several different vascular beds and persists even in the presence of diabetes.

RESEARCH DESIGN AND METHODS

— The current study evaluated individuals participating in a seven-site substudy of the Veterans Affairs (VA) Cooperative Study of Glycemic Control and Complications in Diabetes Mellitus Type 2 (30). Enrolled subjects included male and female veterans over age 40 years who had poorly controlled type 2 diabetes (HbA_{1c} >7.5%) and were being treated with oral agents and/or insulin. Additional exclusion and inclusion criteria have been previously described in detail (30). As part of the baseline exams for the VA Cooperative Study, all subjects were queried regarding their medical history, current health, medication use, and basic socioeconomic information. Subjects also completed questionnaires to assess typical lifestyle behaviors, including alcohol and tobacco use and exercise patterns; received physical examinations; and had blood drawn in the fasting state for assessment of baseline health and a variety of cardiovascular risk factors. In addition, 312 subjects at seven sites (representing >95% of all subjects recruited into the parent study at these sites over the time frame of the substudy) also agreed to receive coronary and abdominal calcium scans during the baseline period. At the enrollment visit, subjects were provided with sufficient information regarding the study goals and methodology to permit them to provide an informed consent. The study protocol was approved by the Carl T. Hayden Phoenix Veterans Affairs Institutional Committee on Human Research.

Individuals were classified as Hispanic or NHW if, in response to U.S. census questions (31), they identified themselves as being Hispanic (or Latino) or NHW, respectively. Height, weight, and waist circumference were measured to the nearest 0.1 cm or 0.5 kg, respectively, and BMI (kg/m^2) was calculated. Resting blood pressure was measured three times in the right arm with the subject having been seated for 5 min. While subjects were in the fasted state, blood was drawn; plasma and serum aliquots were prepared and frozen at −80°C for measurement of standard and novel cardiovascular risk factors. CVD was defined as the presence of prior myocardial infarction (MI), stroke, coronary bypass, or other invasive intervention procedures for coronary artery disease or peripheral vascular disease (PVD) as previously assessed and defined (30). PVD for this study was defined as an ankle brachial index ≤0.9.

All subjects underwent EBCT cardiac scanning using an Imatron C 150XL computer-assisted tomographic scanner (GE Imatron, San Francisco, CA). Starting at the level of the carina and continuing to the level of the diaphragm, 30–40 adjacent, 3-mm−thick axial scan slices were obtained by table incrementation. The entire sequence of scans was acquired during one breath-holding sequence, and tomographic images were electocardiographically triggered to 80% of the RR interval (near the end of diastole) to minimize cardiac motion. To reduce interassay variability of CAC scans, two scans were done in succession on each subject at baseline and the results were averaged. Abdominal aortic scans were obtained by scanning a section of the aorta extending from the upper pole of the right kidney to the iliac bifurcation with 30 adjacent, 6-mm−thick axial slices. A calibration phantom containing four bars of hydroxyapatite of identical physical density was scanned under the chests and abdomens of each participant at each scanning center. This allowed calibration of the images to identical standards.

Readers at the centralized reading center, who were blind to the demographic, clinical, and electrocardiographic information and to the scan pairs, performed calcium scoring. Before the scans were read, the brightness of the images was adjusted (calibrated) to a standard brightness using linear regression against the brightness measured in regions of interest inside the hydroxyapatite bars in the calibration phantom. A computed tomography volume threshold, defined as

volume = slice thickness (3 mm)
× pixel length (0.6836)
× pixel length× minimal lesion size
(four pixels)

was used to identify calcific lesions. The volume threshold for detecting abdominal artery calcium (AAC) lesions was calculated based on the formula

volume = slice thickness (6 mm)
× pixel length (0.5859)
× pixel length × minimal lesion size
(three pixels)

Each focus exceeding the minimum volume criteria (5.6 and 6.18 for CAC and AAC, respectively) and having >130 Hounsfield units was scored using the algorithm developed by Agatston et al. (32). A total coronary calcium score was determined by summing individual lesion scores from each of four anatomic sites (left main, left anterior descending, circumflex, and right coronary arteries). A total aortic calcium score was determined by summing individual lesion scores along the scanned aortic section.

Plasma total cholesterol, triglyceride, and HDL cholesterol concentrations were measured using standard enzymatic methods and reagents obtained from Roche Diagnostics (Indianapolis, IN) on a Hitachi 911 analyzer. Fibrinogen and plasminogen-activating factor 1 (PAI-1) were measured by the Tufts Lipid Metabolism Laboratory in their capacity as the central biochemistry laboratory for the VA Cooperative Study. Fibrinogen was measured by a standard kit assay (Dade Behring) that is based on the relation of plasma clotting time to fibrinogen concentration. PAI-1 mass was measured on platelet-depleted plasma by a kit assay using a monoclonal/polyclonal sandwich enzyme-linked immunosorbent assay kit (American Diagnostica, Stamford, CT). For both assays, intra-assay precision was 2.5–6% and interassay precision was 6–8%.

Statistical methods. Categorical data are presented in percent and continuous data as means ± SD. Calcium scores and log-transformed calcium scores (after adding 1 to each CAC or AAC score) were analyzed. Comparisons between groups were tested by unpaired *t* tests or χ^2 tests for categorical variables. In addition, adjusted CAC and AAC scores were obtained by multiple linear regression analyses, with the Agatston calcium score as the dependent variable and age, years of diabetes duration, years of smoking, and the presence of CVD as independent variables. In additional regression models, lipid and HbA_{1c} variables were included along with the above variables and analyses were repeated for the adjusted

Table 1—*Characteristics of the study population*

Characteristics	Hispanic	NHW	*P*
n	58	187	—
Age (years)	59 ± 9	62 ± 10	$P < 0.05$
Duration of diabetes (years)	10.0 ± 6.1	12.0 ± 7.4	NS
BMI (kg/m^2)	31.5 ± 4.3	31.6 ± 4.3	NS
History of CVD (%)	21 ± 41	40 ± 49	$P < 0.05$
Current smoker (%)	19 ± 5.3	13 ± 2.5	NS
Duration of smoking (years)	20 ± 2.1	27 ± 1.2	$P < 0.05$
Systolic blood pressure (mmHg)	137 ± 20	131 ± 18	NS
Diastolic blood pressure (mmHg)	78 ± 13	74 ± 11	NS
HbA_{1c} (%)	9.5 ± 1.4	9.1 ± 1.4	$P < 0.05$
Total cholesterol (mg/dl)	193 ± 39	187 ± 37	NS
HDL cholesterol (mg/dl)	40 ± 8.2	40 ± 11.4	NS
LDL cholesterol (mg/dl)	112 ± 33	105 ± 29	NS
Triglycerides (mg/dl)	208 ± 101	222 ± 150	NS

Data are means ± SD.

CAC and AAC scores. All tests of significance were two tailed and statistical significance was defined as $P \leq 0.05$.

RESULTS — In all, 245 subjects (58 Hispanics and 187 NHW) completed the substudy and have complete baseline data. Of those, 35% had baseline evidence of atherosclerotic disease, including MI, stroke, bypass surgery, revascularization procedures, or PVD. Subject characteristics and several standard cardiovascular risk factors are shown by ethnic group in Table 1. Age was modestly, but significantly, lower in Hispanic subjects (59 vs. 62 years; $P < 0.05$) and the level of glycemic control (HbA_{1c}) was worse in Hispanics ($P < 0.05$). BMI, waist circumference, duration of diabetes, blood pressure, and lipid levels were not significantly different between the groups. Current and past smoking frequency was modestly (but not significantly) higher in Hispanics, although average total years of smoking was higher in NHWs (20 vs. 27 years; $P < 0.05$). Several novel cardiovascular risk factors were also measured, including PAI-1 and fibrinogen, but those values did not differ between ethnic groups (data not shown). The prevalence of atherosclerotic CVD (MI, revascularization, stroke, or PVD) was significantly less in Hispanics (Table 1).

A careful comparison of socioeconomic factors was also performed. A greater percentage of Hispanics subjects had a high school degree (78 vs. 70%), whereas fewer had received a college education (18 vs. 23%) but neither of these differences was statistically significant. More Hispanics were currently unemployed (19 vs. 5%; $P < 0.05$), but a similar percentage were retired or working full time. Alcohol consumption and frequency of regular exercise did not differ between the groups. Medication use was common in both ethnic groups, but no statistical differences in frequency of use of aspirin, statins, lipid-lowering medications in general, ACE inhibitors, or other blood pressure medications were noted. The use of β-blockers was, however, more common in NHW subjects (37 vs. 21; $P < 0.05$). Similar percentages of subjects in both groups were using insulin (58 vs. 60%), metformin (72 vs. 67%), oral sulfonylureas (49 vs. 52%), and/or thiazolidinediones (8 vs. 11%); none of these differences was statistically significant.

Despite the fact that subjects in both groups appeared to have had diabetes for similar lengths of time, the extent of arterial calcification was reduced in Hispanics (Table 2). Mean and median levels of CAC, as well as 25th and 75th percentile scores, were all lower in Hispanics. Similarly, mean, median, and 25th and 75th percentile AAC scores were lower in Hispanics than in NHW subjects. In patients with no known CVD, mean Hispanic and NHW CAC scores remained strikingly different (53 vs. 139; $P < 0.05$), as did mean AAC scores (346 vs. 727; $P < 0.05$). Figure 1*A* shows that Hispanics had a significantly different overall distribution of CAC scores compared with NHWs ($\chi^2 = 16$, $P < 0.01$), a higher percentage of subjects with very low CAC scores (0–10; $P < 0.05$) and a lower percentage of subjects with CAC scores that are generally equated with extensive atherosclerotic burden (>400; $P < 0.05$). Moreover, the percentage of NHW subjects with CAC scores in the highest two categories was significantly greater than the percentage of Hispanic subjects ($P < 0.01$). Hispanics also demonstrated a different overall distribution of AAC scores compared with NHWs (Fig. 1*B*). For Fig. 1*B*, overall quartiles of AAC were used to compare vascular calcium between Hispanics and NHWs. Again, the two distributions were significantly different ($\chi^2 = 17$, $P < 0.01$), with the percentage of NHW subjects having AAC scores in the highest two quartiles being significantly greater than the percentage of Hispanic subjects ($P < 0.01$).

Within the whole population, log CAC and log AAC levels were positively related to age (CAC: $r = 0.26$, $P < 0.01$; AAC: $r = 0.46$, $P < 0.01$), duration of diabetes (CAC: $r = 0.12$, $P < 0.01$; AAC: $r = 0.23$, $P < 0.01$), and years of smoking (CAC: $r = 0.17$, $P < 0.01$; AAC: $r = 0.30$, $P < 0.01$), but were not strongly related to most other standard risk factors. These same trends were also apparent within each ethnic group, as mean values for age, diabetes duration, and years of smoking increased across increasing quintiles of CAC and AAC (data not shown).

To determine whether differences in CAC and AAC between ethnic groups

Table 2—*Calcification score distributions by ethnicity*

	Hispanic	NHW
CAC scores		
Mean	106	221*
Median	19	93
Minimum	0	0
25th percentile	2	14
75th percentile	82	262
Maximum	1,058	2,541
AAC scores		
Mean	424	945*
Median	117	590
Minimum	0	0
25th percentile	57	66
75th percentile	471	1,412
Maximum	3,046	5,289

*$P < 0.05$. Other parameters were not statistically compared.

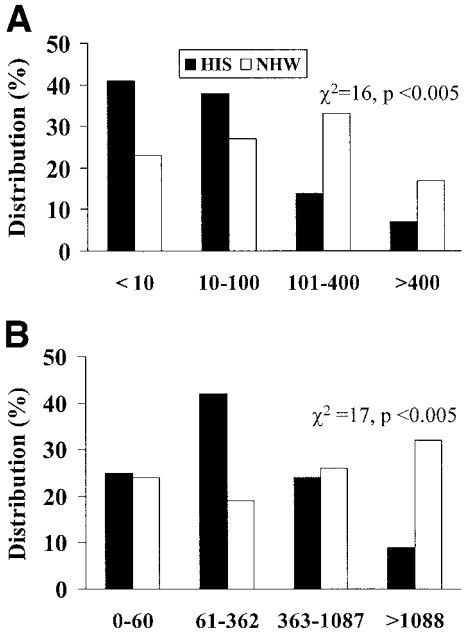

Figure 1—*The distribution of CAC and AAC scores for each ethnic group. The percent of individuals with scores within each presented CAC (A) or AAC (B) range are shown for each ethnic group (■, Hispanic subjects; □, NHW subjects). The overall distribution of CAC and AAC scores was found to differ significantly by χ^2 analysis (P < 0.05), with fewer Hispanics having scores in the highest two categories (P < 0.05).*

were related to or a reflection of underlying differences in age, duration of diabetes, years of smoking, or presence of CVD, several analyses were performed. First, subjects were divided into two strata (low and high) based on the median values for the cohort for the variables age, duration of diabetes, or years of smoking to see if ethnic differences in vascular calcium persisted within the strata. Mean ethnic CAC and AAC levels were compared within high and low groups as shown in Table 3. Mean CAC and AAC values were lower in Hispanics in both low and high categories of age, duration of diabetes, years of smoking, and CVD strata, and most CAC and AAC differences within each stratum were statistically significant ($P < 0.05$). Average age was similar in the two age strata among Hispanics and NHW, respectively (53 and 54 years in the lower stratum; 69 and 69 years in the higher age stratum) and neither difference was statistically significant. The average duration of diabetes in years was similar for Hispanics and NHWs in the lower duration stratum (5 and 6 years) and the difference was not statistically significant; however, NHWs had a higher mean duration of diabetes than Hispanics in the higher duration stratum (14 and 17 years; $P < 0.05$). Average years of smoking was similar among Hispanics and NHWs in both smoking duration strata (11 and 13 years in the lower years of smoking stratum; 34 and 36 in the higher years of smoking stratum); neither difference was statistically significant. These data indicate that differences between ethnic groups in these variables were unlikely to explain the observed ethnic differences in calcium scores. In addition to stratification by important confounder variables, a linear regression model was used to obtain CAC and AAC values adjusted for age, duration of diabetes, years of smoking, and the presence of CVD for the two ethnic groups. The adjusted CAC scores (164 vs. 203; $P < 0.05$) and AAC scores (667 vs. 872; $P < 0.05$) remained significantly lower in Hispanics. Adjusted CAC scores (137 vs. 208; $P < 0.05$) and AAC scores (588 vs. 811; $P < 0.05$) obtained by expanding the linear regression model to include total cholesterol, HDL, and HbA_{1c} were also significantly lower in Hispanics.

Table 3—*Calcification scores stratified by ethnicity and median age, diabetes duration, years of smoking, and presence of CVD*

	CAC		AAC	
Strata	Hispanic	NHW	Hispanic	NHW
Age (years)				
<61	57	155*	271	472*
≥61	186	275	672	1,334*
Duration of diabetes (years)				
<10	108	175	305	834*
≥10	103	261*	556	1,044*
Smoking (years)				
<25	103	160	430	678
≥25	112	311*	411	1,341*
CVD				
None	53	139*	346	727*
Present	308	346	705	1,293*
Total	106	221*	424	945*

*$P < 0.05$ for Hispanic vs. NHW.

CONCLUSIONS — The major finding of this study is that the accumulation of CAC and AAC is reduced in Hispanics with type 2 diabetes compared with their NHW counterparts. Mean, median, and 25th and 75th percentile CAC scores were substantially lower in Hispanics. A striking difference in the overall distribution of scores between ethnic groups was also present, with fewer Hispanic subjects having CAC >100 or >400. Calcium scores at these levels occur more frequently in those with moderate or severe atherosclerosis, respectively (21). Equally impressive was the fact that AAC (both mean levels and the percentage of subjects with high scores) was also significantly reduced in Hispanics with type 2 diabetes. These data are consistent with two prior reports that nondiabetic Hispanics have less CAC than their NHW counterparts (28,29). Thus, these results strengthen the concept that Hispanics have a reduced extent of arterial calcification. Moreover, this apparent ethnic difference persists even in the presence of poorly controlled diabetes.

Although there is some controversy as to whether Hispanics have fewer CVD events (16–20), studies of carotid intimal medial thickness or peripheral atherosclerosis have consistently found less ath-

erosclerosis in Hispanics compared with NHWs. These data, along with the consistent findings that both CAC and AAC are reduced in Hispanics, suggest that the extent of overall atherosclerosis is reduced in Hispanics compared with their NHW counterparts. The fact that Hispanic subjects in our study also had a reduced prevalence of CVD is consistent with the notion that atherosclerosis is reduced in these individuals. Of note, in analyses excluding or adjusting for individuals with known CVD, CAC and AAC scores were both still significantly lower in Hispanics, indicating that these differences were not explained by a chance enrollment of more subjects with CVD into the NHW group.

It is interesting that the reduced arterial calcification in these Hispanic subjects was present despite the fact that levels of traditional and several nontraditional cardiovascular risk factors were similar between the two ethnic groups. Moreover, despite evidence demonstrating that diabetes is strongly associated with increased vascular calcification (25,33), these ethnic differences persisted in this diabetic population. These facts make the finding of reduced CAC and AAC in Hispanics even more impressive.

Although the explanation for these ethnically related differences in CAC or AAC is unknown, one can speculate about possible mechanisms. Hispanics could have reduced levels of other nontraditional cardiovascular risk factors that have recently been postulated to play important roles in atherogenesis. However, C-reactive protein, perhaps one of the more sensitive and consistent markers of inflammation, is consistently increased in diabetes in both Hispanic and NHW populations (34–36) and is frequently elevated in Hispanics compared with NHWs (29,35). We also demonstrated that other novel risk factors, such as levels of PAI-1 and fibrinogen, were not different between the two ethnic groups. Thus, it appears unlikely that reduced levels of these novel cardiovascular risk factors are responsible for the reduced CAC seen in Hispanics. Alternatively, as a result of environmental or genetic differences, Hispanics may be protected in some fashion from atherosclerosis and vascular calcification, despite an apparently worse cardiovascular risk profile. Although we did not detect substantial differences in socioeconomic characteristics, exercise, or other lifestyle behaviors, careful study of these factors and dietary differences as well as their interaction with specific genetic polymorphisms associated with vascular calcification is needed.

In future studies it will be important to compare multiple measures of subclinical atherosclerosis in the same individuals in different ethnic groups to more carefully determine whether these vascular calcification differences are related to a systemic or vessel-specific protection against atherosclerosis or only reflect a reduced tendency to develop vascular calcification. Although both of these outcomes are important, they have different implications for our understanding of vascular disease and the development of both prevention and therapeutic strategies. In addition, prospective studies will be needed to determine whether ethnic differences in arterial calcification translate into important differences in the development of clinical events.

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