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Relation between Retinopathy and Progression of Coronary Artery Calcium in Individuals with Versus Without Diabetes Mellitus (From the Multi–Ethnic Study of Atherosclerosis)

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Abstract

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Authors Contribution

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Disclosures

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Retinopathy is a microvascular complication of diabetes mellitus (DM); however, it is also increasingly recognized in persons without DM. The microvascular diseases may play a prominent role in coronary heart disease (CHD) development in individuals with DM. We performed the study to evaluate the relation between non-DM retinopathy and CHD and also the association between baseline retinopathy and incidence and progression of CHD in individuals with and without DM. We included 5709 subjects with and without DM from the Multi-Ethnic Study of Atherosclerosis, who had retinal photos and coronary artery calcium score (CACS) available. We studied the association between baseline retinopathy and incidence and progression of coronary artery calcification (CAC) in subjects with and without DM. In DM group, the presence of retinopathy was significantly associated with an increased rate of CAC (RR 1.3 (95% CI [1.02, 1.66]) after adjusting for age, sex, race, follow-up time, and CHD risk factors. In non-DM group, the presence of retinopathy was not significantly associated with increased risk of CAC, however, the interaction between presence of retinopathy and DM status was not statistically significant. Within the DM group with CAC present at baseline, the presence of retinopathy was significantly associated with greater CAC progression (113 Agatson units (AU) greater, (95% CI [51–174]). In the non-DM group with present CAC at baseline; the presence of retinopathy was associated with 24 (95% CI [−0.69, 48.76]) AU higher CAC progression. All findings were adjusted for CHD risk factors. In conclusion, after adjustment for major CHD risk factors, retinopathy was associated with progression of CAC in both DM and non-DM individuals. However, the association was stronger in those with DM.

Background

Diabetic retinopathy is a microvascular complication of diabetes mellitus (DM). DR presents the physician with the unique opportunity to directly visualize anatomical changes and grade the progression of the disease.[1] Retinopathy in persons without DM is thought to be a sign of microvascular disease.[2] Coronary heart disease (CHD) is a leading cause of death, particularly among persons with type 2 DM (DM2).[3] Microvascular disease may play a prominent role in CHD development in individuals with DM[4]. There is an emerging recognition that persons with retinal microvascular signs are at higher risk of cardiovascular diseases (CVD) including stroke and CHD.[5] These findings support the concept that retinal microvascular signs, unique morphologic pathologies directly observable in vivo, may represent new biomarkers of CHD risk. Coronary artery calcification (CAC) is an independent predictor of CHD risk, and retinopathy is reported to associate independently with CAC.[6] Studies have shown independent relation between retinal microaneurysms (MA) and CHD in patients with DM.[1,7] Also, studies have shown a correlation between MA count and progression or regression of DR;[8,9] however, none of these studies have used CAC as an indicator of CHD or associated retinopathy with the progression of CAC. In this study, we associated retinopathy with the incidence and progression of CAC in both DM and non-DM individuals.

Methods

All research involving human participants have been approved by Institutional Review Board at all participating sites. Written informed consent was obtained from the participants

and saved either as a hard copy or an electronic copy in the patient's charts at all participating sites. Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter, prospective cohort study of subclinical CVD. Details about the study design and objectives have been published.[10] Briefly, 6814 men and women from 4 ethnic origins (Caucasian, African American, Hispanic American, and Asian American), aged 45 to 84 years and free of clinically diagnosed CVD, were enrolled from 6 US field centers (Baltimore City/ Baltimore County, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan/the Bronx, NY; and St. Paul, MN). MESA participants who had retinal photographs at Exam 2 were eligible for this study.

Details on the retinal photography protocol and measurements have been published previously[6]. Both eyes were photographed using a 45-degree digital non-mydriatic camera. The images were read at the University of Wisconsin, Madison, and evaluators were masked to the participant's characteristics. Retinal microvascular signs were defined by the Early Treatment DR Study (ETDRS)[11] severity scale. Five retinal signs were considered: 1) Presence of any retinopathy (ETDRS level 14 and higher); 2) ETDRS level 20; microaneurysm (MA) only group; 3) Presence of focal arteriolar narrowing; 4) AV nicking, and 5) Retinal vessel calibers (the central retinal arteriolar equivalent [CRAE] and the central retinal venular equivalent [CRVE]).

Methods of obtaining and interpreting the Computed Tomographic (CT) scans have been published previously[12]. Baseline images were obtained using ECG gating[10] during a single breath-hold by using an ECG-triggered electron-beam CT scanner or prospective ECG-triggered scan acquisition at 50% of the RR interval with a multi-detector computed tomography scanner. All images were read at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (Torrance, CA) as the reading center using an interactive scoring system similar to what has been described by Yaghoubi et al[13] The mean Agatston score obtained from two scans was used in all analyses for each subject.[14] Excellent intra-observer and interobserver agreement (kappa statistics, 0.93, and 0.90, respectively) were achieved. Calcium scores were measured on exam 1 and then on exams 2, 3, and 4 (on 50%, 50%, and 25% of cases respectively), and incidence and progression of coronary artery calcium were measured.

At the baseline visit, age, race/ethnicity, smoking status, medication use, body mass index (BMI) (kg/m^2), and resting blood pressures were recorded. Fasting cholesterol and glucose levels were measured at the collaborative studies' clinical laboratory at Fairview-University Medical Center (Minneapolis, MN). Total and high-density lipoproteincholesterol (TC, HDL-C) were measured using cholesterol oxidase methods. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation when triglyceride <400 mg/dl. Diagnosis of dyslipidemia was based on the set criteria and use of lipid-lowering medications[15]. Serum C-reactive protein (CRP) was measured using the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc, Deerfield, IL) at the Laboratory for Clinical Biochemistry Research, University of Vermont, Burlington, VT. The inter-assay coefficient of variation ranged from 2.1% to 5.7%. Serum Fibrinogen was quantitatively measured by immunoprecipitation of fibrinogen antigen using the BNII nephelometer (N-Antiserum to

Human Fibrinogen, Dade-Behring Inc, Deerfield, IL). Its intra-and inter-assay coefficients of variation were 2.7% and 2.6%, respectively.

Height was measured to the nearest 0.1 cm with the subject in the stocking while weight was measured to the nearest pound with the subject in light clothing using a balanced scale and BMI was calculated by dividing weight in kilograms by height in meters squared. Using a Dinamap model Pro 100 automated sphygmomanometer (Critikon, Tampa, FL); right arm resting seated BP was measured three times at 1-minute intervals with an average of the last two readings used for analysis. Hypertension was defined as receiving antihypertensive medications or a systolic blood pressure (SBP), ≥140 mm Hg or diastolic blood pressure (DBP), ≥90 mm Hg.[16] DM was defined as receiving hypoglycemic medications or fasting blood glucose of ≥126 mg/dl. Measurements for calculation of Ankle Brachial Index (ABI) were obtained using a hand-held Doppler instrument with a 5-MHz probe (Nicolet Vascular, Golden, Colorado). Smoking status was categorized as never, former, or current. We assessed the demographic and socioeconomic data: age, gender, race/ethnicity, income, educational attainment, and marital status. We looked for potential confounders or risk factors, such as cigarette smoking status, pack-years of cigarette smoking; alcohol use, SBP, DBP, waist circumference, BMI, DM medications, TC, HDL-C and LDL-C, triglycerides, and use of lipid-lowering agents.

After excluding the participants missing DM status, evaluation of retinopathy at baseline, or follow-up CT scan for CAC, 5709 participants were included in the analysis. Incident CAC was defined as new onset of CAC at any of the follow-up exams (exam 2 or 3 or 5) among the participants free of detectable CAC at baseline (if a participant had no onset of CAC, he/she was considered to be at risk at the longer follow-up exam); CAC progression as a continuous variable was defined as the difference between the baseline CAC score and the follow-up CAC score according to the longest follow-up time. The association between the presence of retinopathy and progression of CAC was evaluated in both DM and non-DM participants separately and compared between the two groups by testing the interaction between DM status and presence of retinopathy in the pooled sample. The association between the grades of retinopathy (mild, moderate, severe) and progression of CAC was also evaluated in DM and non-DM groups.

Relative risk regression with robust standard models[17] was used to model the probability of incident CAC among those free of CAC at baseline. Since the exact time for incident CAC development was not measured, a relative risk model adjusting for the follow-up time was determined to be more plausible than the survival model. Among those with detectable CAC at baseline, robust regression models were used to model the change in CAC between exams, accounting for the influence of outliers. CAC progression was modeled while adjusting for the follow-up time, an analogous approach as the model for incident CAC.

Four sets of statistical models for retinopathy were built, ranging from the simplest model to the most complicated ones: adjusting for demographics including age, sex, race, and follow-up time (model A); adjusting for variables in model A plus CHD risk factors including SBP, TC, HDL-C, LDL-C, triglycerides, anti-hypertensive medications, lipid-lowering

medications, smoking (model B); adjusting for variables in model B plus other CHD risk factors and inflammatory markers including BMI, the logarithm of CRP, fibrinogen, the logarithm of HbA1c, the logarithm of creatinine, fasting blood glucose, albuminuria, ABI, use of insulin or oral hypoglycemics and family history of myocardial infarction (model C); adjusting for variables in model C plus CRAE and CRVE (model D). We used Model B as our primary model while used Model C/D to evaluate how the association would be attenuated by other CHD risk factors and CRAE/CRVE. All analyses were conducted using R version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.2 (SAS Institute Inc, Cary, NC).

Results

From MESA visit 2 data (immediately after baseline visit), there are 619 subjects with retinopathy based on their most severely affected eye (~65% of whom had both eyes affected). The baseline characteristics for all four groups have been shown in Table 1. Sample sizes for 4 different groups based on presence and absence of retinopathy and/or DM were 248 retinopathy +DM+, 602 retinopathy –DM+, 371 retinopathy retinopathy +DM−, and 4488 retinopathy −DM− respectively. On the eye exam, retinopathy +DM+ individuals were more likely to have pure MAs and CRAE while retinopathy +DM− were also more likely to have MAs only, AV nicking, and CRAE. In the non-DM group, those with retinopathy were more likely to have CACS >0 (Table 1).

For DM individuals, the presence of retinopathy was significantly associated with greater CAC incidence (relative risk of 1.35 (95% CI [1.07, 1.7]) after adjusting for age, gender, race/ethnicity, and follow-up time. This association was significant for Model B (RR 1.3, 95% CI [1.02, 1.66]) as well. In the non-DM individuals, however, the presence of retinopathy was not significantly associated with incident CAC in any of the multivariable models. However, the interaction between the presence of retinopathy and DM status was not significant in any of the models, indicating that the association of retinopathy with incident CAC was not statistically significantly different between DM and non-DM individuals (Table 2).

Within the DM group, the presence of retinopathy was significantly associated with CAC progression in all adjustment models. Similarly, within the non-DM group, the presence of retinopathy was associated with 24.03 (95% CI [−0.69, 48.76]) Agatston units higher CAC progression in Model B and yielded similar values after adjusting for variables in other models. The interaction between the prevalence of retinopathy and DM status was significant in Model A and B indicating that the association of retinopathy with the progression of CAC was greater within the DM group than the non-DM group. However, this interaction was not significant after adjusting for other risk-factors in Model C and D which might indicate associations are independent of major conventional CHD risk factors. (Table 3, Figure 1)

We repeated the analysis for MA only. The Presence of MA was not associated with an incidence or progression of CAC in DM or non-DM individuals. We analyzed the association of grades of retinopathy with incidence and progression of CAC among those

with zero CAC and positive CAC at baseline from robust regression models. The grades of retinopathy were defined as: none, minimal non-proliferative (ETDRS level 14 −20), early to moderate non-proliferative (ETDRS level 31–41), and severe non-proliferative or proliferative (level 51–80). Among those with zero CAC, in the DM group, early to moderate and severe NPDR had significantly higher incident CAC risk than the non-retinopathy group. The minimal NPDR group had a similar incident CAC risk as the non-retinopathy group. Among those with positive CAC at baseline, in the DM group, the early to moderate NPDR group had higher CAC progression than the non- retinopathy group. In the non-DM group, the minimal NPDR group had significantly higher CAC progression than the non- retinopathy group (Data are available in a supplementary article).

We also analyzed the association of AV nicking and focal arteriolar narrowing with incidence and progression of CAC among those with zero and positive CAC at baseline, however, no association was seen between AV nicking and focal arteriolar narrowing with the incidence and progression of CAC (data not shown).

Discussion

The current study demonstrated that among DM and non-DM individuals who were free of clinical CHD, retinopathy was associated with progression of CAC, an indicator of CAD, however, this association was stronger in those with DM compared to those without. The association was present after adjusting for major CHD risk factors indicating its independence from major CHD risk factors. CAC is an independent predictor of CHD risk and represents subclinical CHD. In a previous cross-sectional analysis in MESA, there were significant associations between retinal microvascular signs and CAC.[6] What remained unclear is whether these retinal microvascular signs are associated with the incidence or progression of CHD, independent of risk indicators of CHD. In the Atherosclerosis Risk in Communities study,[17,18] it was shown that in persons with DM2, the presence of retinopathy was associated with a two-fold higher risk of incident CHD and a three-fold higher risk of fatal CHD, independent of glycemic levels, cardiovascular risk factors and large vessel atherosclerosis. This association was significant in men and women, and in those without Hypertension. While associations were seen for most retinopathy lesions, they were statistically significant only for retinal MAs. In our study, however, we did not find an association of MAs with incidence and progression of CAC.

Studies have shown that DM individuals with retinopathy are more likely to have myocardial perfusion abnormalities[19], poorer coronary flow reserve[20], and lower coronary collateral development[21] than those without retinopathy. Moreover, DR has also been associated with higher degrees of coronary calcification[22], and more diffuse and severe coronary artery stenosis on angiograms.[23] These observations support the concept that microvascular and macrovascular complications of DM may share common pathogenic mechanisms.[24,25] It is uncertain what these pathways may be (e.g., endothelial dysfunction, oxidative stress, and platelet dysfunction), but one potential candidate that has gained recent interest involves the advanced glycation end-products, which can cause both microvascular and macro-vascular injury in DM.[25,26]

In physiological conditions, vasa vasorum (VV) provides oxygen and nutrients to the arterial wall. Hyperglycemia alters the structure of the VV in individuals with DM.[27] Studies have shown that in patients with DM, the VV undergoes pathologic changes initially with endothelial dysfunction and loss of capillaries; and in more advanced stages with ischemia leading to angiogenesis and plaque neovascularization.[28] Thus, atherosclerosis is promoted by abnormalities in the capillary rich VV of the conductance vessels. Similar findings have been seen in retina and kidneys in patients with DM. This common pathophysiologic pathway may explain why coronary atherosclerosis is more severe in patients with DR as evidenced by higher CACs.[29]

CAD, which often remains asymptomatic for a long period of time, is a leading cause of morbidity and mortality in patients with DM2. Timely diagnosis of CAD and appropriate monitoring of its progression is of great importance in patients with DM2.[3] According to the results of the present study, in patients with DM2; the presence of DR is associated with significant progression of CAC as a marker of CAD. Retinal examination is a simple, noninvasive, and routinely employed test used in the follow-up of these patients. By using this simple test as a screening method, the clinicians can distinguish patients who need further evaluation for CAD, enabling earlier detection of CAD. This study suggests that CAD may be investigated once DR is diagnosed in a patient with DM2.

There are also some limitations of this study. Subtle differences in prevalence and risk factors of retinopathy in MESA compared with other studies may be related to differences in retinal photography such as 45 degrees non-stereoscopic digital photographs were taken without pharmacological dilation in MESA, as compared with 30 degrees stereoscopic film-based photographs taken with pharmacological mydriasis in some other studies.[30] Exclusion of persons with symptomatic CVD in MESA could also have operated differently across ethnic groups as a result of differences in access to care and diagnosis of disease. Lastly, we find that missing data is higher for the DM group with zero CAC at baseline than the non-DM group, secondary to more dropouts at exam 5 in the DM group which may indicate poorer health in the DM group. However, these groups had similar baseline characteristics and there was no difference in missing data neither for people with and without DM nor for those with and without retinopathy among those with positive CAC at baseline. The incidence of new retinopathy in those with progression in CAC was not studied separately in our study. Further study is needed to address this issue.

Conclusion

Our study has found that, in a multiethnic cohort, retinopathy was associated with progression of CAC more significantly in those with DM compared to those without; and may suggest that DM patients with retinopathy would benefit from more intense CVD risk factor modification and closer monitoring to prevent progression of CHD.

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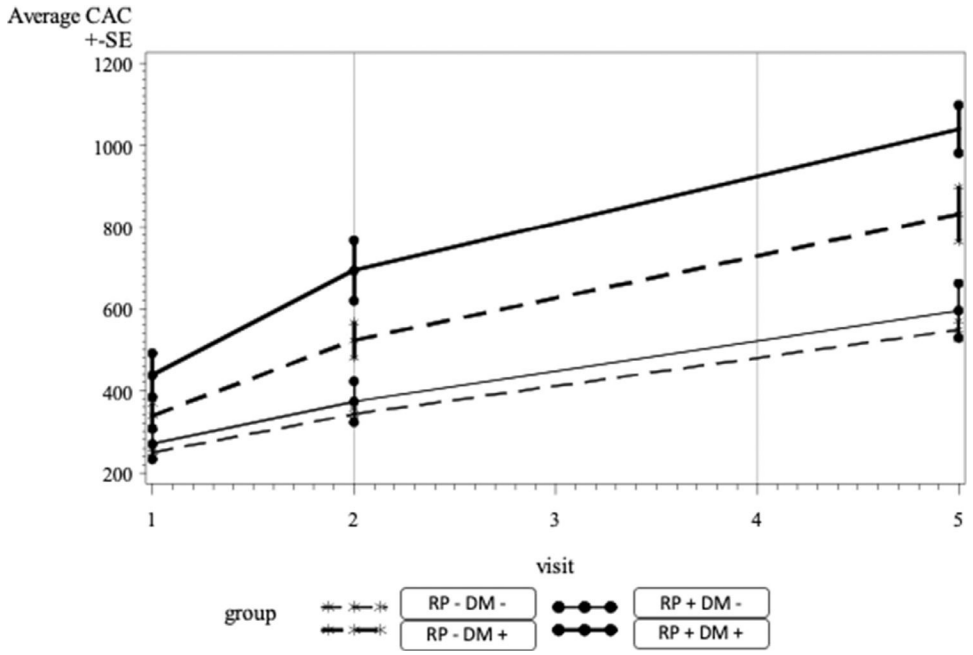

Figure 1.

represent the progression of CAC among those with positive CAC at baseline by retinopathy status among individuals with and without DM in four sets of statistical models for adjusting various factors: demographic characteristics, CHD risk factors, and retinal vessel calibers. In both DM and non-DM group, the presence of retinopathy was significantly associated with CAC progression in all adjustment models.

Table 1

Distribution of baseline characteristics (mean (SD) or frequency (%)) for combinations of diabetes mellitus and retinopathy status

	Diabetes Mellitus					
	Yes			No		
Variables	**Retinopathy (n = 248)**	**No retinopathy (n = 602)**	**p***	**Retinopathy* (n = 371)**	**No retinopathy (n = 4488)**	**p**
Age (Years)	63.3 (9.5%)	63.7 (9.3%)	0.50	61.7 (10 %)	61.2 (10.1%)	0.361
Men	131 (52.8%)	316 (52.5%)	0.99	195 (52.6%)	2090 (46.6%)	0.03
White	40 (16.1%)	155 (25.7%)		149 (40.2%)	1932 (43%)	
Chinese American	25 (10.15)	73 (12.1%)		59 (15.9%)	522 (11.6%)	
Black	101 (40.7%)	204 (33.9%)		101 (27.2%)	1125 (25.1%)	
Hispanic	82 (33.1%)	170 (28.2%)	0.01	62 (16.7%)	909 (20.3%)	0.034
Income >25 k	134 (57%)	353 (61.4%)	0.29	257 (71%)	3173 (73%)	0.443
Education (high school or less as reference)						
Some college	75 (30.2%)	161 (26.7%)		116 (31.4%)	1279 (28.6%)	
Bachelor's degree	30 (12.1%)	89 (14.8%)		48 (13%)	867 (19.4%)	
Graduate/ professional degree	27 (10.9%)	73 (12.1%)	0.59	82 (22.2%)	904 (20.2%)	0.026
Single/Divorced	134 (54%)	366 (61.1%)	0.07	227 (61.5%)	2783 (62.8%)	0.667
Waist Circumstance (cm)	105 (14.61%)	105 (13.82%)	0.1	98.3 (13.8%)	96.6 (14%)	0.02
BMI (Kg/m^2)	30.3 (5.78%)	30.8 (5.79%)	0.22	28.6 (5.4%)	27.8(5.2%)	0.014
Smoker (never as reference)						
Former	90 (36.3%)	240 (39.9%)		128 (34.6%)	1644 (36.7%)	
Current	25 (10.1%)	78 (13%)	0.195	49 (13.2%)	552 (12.3%)	0.683
Cigarette PY	9.19 (18.89%)	13.53 (235)	0.005	9.9 (18.2%)	10.9 (22.6%)	0.314
Alcohol use (never as reference)						
Former	91 (37%)	186 (30.9%)		79 (21.6%)	935 (21%)	
Current	91 (37%)	284 (47.3%)	0.024	212 (60%)	2660 (60%)	0.796
SBP (mm Hg)	191.7 (44.3%)	188.9 (37.2%)	0.061	131 (21.6%)	124 (20.6%)	<0.001
DBP (mm Hg)	46.4 (12.2%)	45.8 (12.3%)	0.289	75.2 (10.5%)	71.6 (10.8%)	<0.001
HR (bpm)	114.5 (34.3%)	111.7 (32.9%)	0.006	55.8 (16.7%)	52.6 (16.4%)	<0.001
Total cholesterol (mg/dl)	4.9 (0.6%)	4.9 (0.6%)	0.368	194.6 (34.1%)	195 (34.6%)	0.825

Variables	Diabetes Mellitus					
	Yes			No		
	Retinopathy (n = 248)	No retinopathy (n = 602)	p*	Retinopathy* (n = 371)	No retinopathy (n = 4488)	p
HDL (mg/dl)	0.95 (1.2%)	0.9 (1.2%)	0.479	49.8 (13.7%)	52.1 (15%)	0.002
LDL (mg/dl)	374.5 (83.3%)	356.8 (77.5%)	0.286	120.3 (31%)	117.9 (30.5%)	0.142
Triglycerides, log	2 (0.2%)	1.9 (0.2%)	0.137	4.7 (0.5%)	4.7 (0.5%)	0.96
CRP, log	−0.1 (0.3%)	−0.1 (0.3%)	0.38	0.6 (1.3%)	0.6 (1.14%)	0.978
Fibrinogen mg/dl	160.3 (65.7%)	131.4 (39.6%)	0.004	345.6 (70.9%)	340.8 (70.19%)	0.212
HbA1c, log	134 (22.9)	130.9 (19.7)	<0.001	1.7 (0.08)	1.7 (0.08)	0.142
Creatinine, log	71.7 (10.71%)	72.5 (10.12%)	0.544	−0.05 (0.2%)	−0.07 (0.21%)	0.122
FBS (mg/dL)	62.3 (20.07%)	58.3 (15.9%)	<0.001	90.8 (10%)	88.5 (9.67%)	<0.001
Microalbuminuria mcg/min	63 (25.7%)	88 (14.7%)		21 (5.7%)	234 (5.2%)	
Macroalbuminuria mcg/min	16 (6.5%)	19 (3.2%)	0	2 (0.5%)	22 (0.5%)	0.933
ABI	1.1 (0.16%)	1.1 (0.13%)	0.736	1.1 (0.1%)	1.1 (0.1%)	0.316
Use of anti-hypertension medications	159 (64.1%)	350 (58.3%)	0.137	145 (39.1%)	1403 (31.3%)	0.002
Use of lipid-lowering medications	68 (27.4%)	159 (26.5%)	0.849	57 (15.4%)	634 (14.1%)	0.564
Use of insulin or oral hypoglycemics	196 (79%)	319 (54.2%)	<0.001	1 (0.3%)	13 (0.3%)	1
Family history of MI	102 (44%)	237 (42.6%)	0.789	153 (44%)	1787 (42.2%)	0.565
Exam 1 CAC >0	157 (63.3%)	347 (57.6%)	0.147	194 (52.3%)	2047 (45.6%)	0.015
Exam 1 average CACS for those with positive CAC	438 (670.9)	339.5 (553)	0.109	270.5 (517.8)	249 (476)	0.578
MA only; worse eye	111 (66.1 %)	2 (0.3 %)	<0.001	234 (64.1 %)	14 (0.3%)	<0.001
AV nicking	12 (4.9 %)	35 (5.8 %)	0.7	28 (7.5 %)	160 (3.6 %)	<0.001
Focal arteriolar Narrowing	0	2 (0.3%)	0.9	9 (2.4 %)	38 (0.9 %)	0.007
CRAE	146 (13.4%)	145.1 (13.9%)	0.375	142.3 (13.7%)	144.2 (14.1%)	0.012
CRVE	224 (25.3%)	217.2 (22.7%)	<0.001	212.6 (22.3%)	213.4 (21.3%)	0.533

ABI = ankle brachial index; AV = arterio-venous, Bpm = beats per minute; BMI = body mass index; CAC = coronary artery calcification; CACS = coronary artery calcium score; CRAE = central retinal arteriolar equivalent; CRP = C-reactive protein; CRVE = central retinal venular equivalent; DBP = diastolic blood pressure; FBS = fasting blood sugar; HDL = high density lipoprotein cholesterol; HbA1c = hemoglobin A1c; Kg/m^2 = kilograms per square of the height in meters; Log = logarithm; LDL = low density lipoprotein cholesterol; MA = retinal microaneurysms, mcg/min = *micrograms per minutes*; MI = myocardial infarction; mg/dl = milligrams per deciliter; mm Hg = millimeters of mercury; PY = pack year; SBP = systolic blood pressure.

*T test for continuous variable and Chi-square test for discrete variables.

Table 2

The association of retinopathy and incident CAC among those with zero CAC at baseline

		Cumulative incidence (%; n at risk)	Model A*, relative incident ratio (95% CI)	Model B**, relative incident ratio (95% CI)	Model C+, relative incident ratio (95% CI)	Model D++, relative incident ratio (95% CI)
DM	RP absent	42% (255)	1.00	1.00	1.00	1.00
	RP present	55% (91)	1.4 (1.1,1.7)	1.3 (1,1.7)	1.2 (0.9,1.5)	1.2 (0.91,1.59)
Non-DM	RP absent	32% (24)	1.0	1.0	1.00	1.00
	RP present	37% (177)	1.1 (0.9,1.4)	1.1 (0.91,1.32)	1.1 (0.9,1.3)	1.09 (0.9,1.31)
Interaction between retinopathy and DM p value	-		0.1466	0.1711	0.6348	0.6392

ABI = ankle brachial index; BMI = body mass index; CAC = coronary artery calcification; CRAE = central retinal arteriolar equivalent; CRP = C-reactive protein; CRVE = central retinal venular equivalent; DM = diabetes mellitus; HbA1c = hemoglobin A1c HDL = high density lipoprotein cholesterol; Log = logarithm; MI = myocardial infarction; RP = retinopathy; SBP = systolic blood pressure.

*Adjusted for age, gender, race, and follow up time.

**Adjusted for variables in model a plus cardiovascular risk factors including total cholesterol, HDL-C, log of triglycerides, lipid-lowering medications, SBP, anti-hypertension medications, smoking status and cigarette pack-years.

+Adjusted for variables in model B plus and BMI, log of CRP, Fibrinogen, log of HbA1C, log of creatinine, glucose, albuminuria, ABI, use of insulin or oral hypoglycemics and family history of MI.

++Adjusted for variables in model C and CRAE and CRVE.

Table 3

The association of DM retinopathy and progression of CAC (AU) among those with positive CAC at baseline

		Average CAC progression per year (SD)	Model A*, difference in average CAC progression (95% CI)	Model B** difference in average CAC progression (95% CI)	Model C+ difference in average CAC progression (95% CI)	Model D++ difference in average CAC progression (95% CI)
DM	RP absent	68.2 (95.5)	Ref	Ref	Ref	Ref
	RP present	96 (117.4)	102.9 (45.7, 160.1)	112.6 (51, 174.2)	88.1 (14.2, 161.9)	78.3 (2, 154.6)
No-DM	RP absent	37.5 (62.8)	Ref	Ref	Ref	Ref
	RP present	44.1 (71.5)	27.1 (2.9, 51.2)	24.03 (−0.7, 48.8)	30 (3.6, 56.2)	30.53 (4.1, 57)
Interaction between RP and DM, p value	-		0.0096	0.005	0.149	0.2076

ABI = ankle brachial index; AU = agatston units; BMI = body mass index; CAC = coronary artery calcification; CRAE = central retinal arteriolar equivalent; CRP = c-reactive protein; CRVE = central retinal venular equivalent; DM = diabetes mellitus; HbA1c = hemoglobin A1c; HDL = high density lipoprotein cholesterol; Log = logarithm; MI = myocardial infarction; No-DM = no diabetes mellitus; Ref=reference; RP = retinopathy; SBP = systolic blood pressure.

*Adjusted for age, gender, race, follow up time

**Adjusted for variables in model A plus cardiovascular risk factors including total cholesterol, HDL, log of triglycerides, lipid-lowering medications, SBP, anti-hypertension medications, smoking status and cigarette pack-years

+Adjusted for variables in model B plus and BMI, log of CRP, Fibrinogen, log of HbA1C, log of creatinine, glucose, albuminuria, ABI, use of insulin or oral hypoglycemics and family history of MI

++Adjusted for variables in model C and central retinal arteriolar equivalent CRAE and CRVE