Hemoglobin A_{1c} and the Progression of Coronary Artery Calcification Among Adults Without Diabetes

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

Higher levels of hemoglobin A_{1c} (HbA_{1c}) are associated with increased cardiovascular disease risk among individuals without diabetes and may also be positively associated with coronary artery calcification (CAC). This study investigated the association of HbA_{1c} with CAC progression in the Coronary Artery Risk Development in Young Adults study.

RESEARCH DESIGN AND METHODS

We included 2,076 participants with HbA_{1c} and noncontrast computed tomography (CT) assessed at baseline (2005–2006), and CT repeated 5 years later (2010–2011). CAC progression was defined as *1*) incident CAC (increase >0 Agatston units among those with no CAC at baseline), *2*) any CAC progression (increase >10 Agatston units between examinations), and *3*) advanced CAC progression (increase >100 Agatston units between examinations).

RESULTS

During the 5-year follow-up period, 12.9% of participants without baseline CAC developed incident CAC; among all participants, 18.2% had any CAC progression and 5.4% had advanced CAC progression. Higher HbA_{1c} was associated with incident CAC (risk ratio [RR] = 1.45; 95% CI 1.02, 2.06), any CAC progression (RR = 1.51; 95% CI 1.16, 1.96), and advanced CAC progression (RR = 2.42; 95% CI 1.47, 3.99) after adjustment for sociodemographic factors. Additional adjustment for cardiovascular risk factors attenuated the associations of HbA_{1c} with incident CAC (RR = 1.05; 95% CI 0.74, 1.49) and any CAC progression (RR = 1.13; 95% CI 0.87, 1.47). In contrast, the association of HbA_{1c} with advanced CAC progression persisted in multivariable adjusted models (RR = 1.78; 95% CI 1.08, 2.95).

CONCLUSIONS

Higher HbA_{1c} was independently associated with advanced CAC progression among individuals without diabetes, while the associations with incident CAC and any CAC progression were accounted for by other established cardiovascular risk factors.

Higher hemoglobin A_{1c} (HbA_{1c}) has been associated with an increased risk of cardiovascular morbidity among individuals without diabetes (1–3). A potential pathway linking HbA_{1c} and cardiovascular events involves the development and progression of subclinical atherosclerosis. The atherosclerotic process begins early

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in life (4), and noninvasive markers of subclinical atherosclerosis, such as coronary artery calcification (CAC), can be used to identify individuals earlier in the disease process who may have an increased risk of clinical events later in life. CAC has been shown to be a predictor of incident cardiovascular events (5–7), but the association of HbA_{1c} with CAC among individuals without diabetes is not clear.

Prior studies of the association between HbA_{1c} and CAC were cross-sectional and reported contrasting findings for individuals without diabetes (8–10). To date, the relation of HbA_{1c} and CAC progression among individuals without diabetes has not been reported in the literature. The purpose of this study was to investigate the prospective association of HbA_{1c} with 5-year CAC progression among individuals without diabetes from the Coronary Artery Risk Development in Young Adults (CARDIA) Study.

RESEARCH DESIGN AND METHODS

Study Design and Population

CARDIA is a prospective, community-based cohort study of young adults designed to investigate trends and determinants of cardiovascular disease risk in the U.S. A detailed overview of the study design, recruitment, and objectives has been previously published (11).

Briefly, the baseline examination (1985–1986) included 5,115 non-Hispanic African American and white men and women aged 18–30 years from Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. This analysis used data from in-person follow-up examinations at 20 (2005–2006) and 25 (2010–2011) years following the baseline examination. Participant retention rates were high, with 72% (n = 3,549) of surviving participants completing the year 20 examination (baseline for this analysis) and 72% (n = 3,498) of the surviving participants completing the year 25 examination (follow-up for this analysis). Centralized training and certification, standardized methods, and quality control measures were implemented to ensure high data quality for all examinations. The institutional review board at each participating site approved the protocol for each study examination, and participants provided written informed consent at each study examination.

For our analysis, we excluded participants who did not attend both the year 20 and the year 25 examinations (n = 1,993), did not have HbA_{1c} measured at the year 20 examination (n = 367), did not have CAC measured at the year 20 (n = 225) and year 25 (n = 149) examinations, or had diabetes (n = 283). Diabetes was defined as a fasting glucose $\geq$126 mg/dL, 2-h postchallenge glucose $\geq$200 mg/dL, HbA_{1c} $\geq$6.5% (48 mmol/mol), or use of antihyperglycemic therapy. Additionally, 22 participants with an estimated glomerular filtration rate $<$30 mL/min/1.73 m^2 or an adjudicated myocardial infarction were excluded. The sample size for the analysis of any CAC progression and advanced CAC progression was 2,076 participants. For incident CAC, those with prevalent CAC at the year 20 examination were excluded, resulting in a sample size of 1,693 for that analysis.

HbA_{1c}

HbA_{1c} was measured from a whole-blood aliquot by ion-exchange high-performance liquid chromatography (Tosoh G7) at the University of Minnesota as part of the Young Adult Longitudinal Trends in Antioxidants ancillary study at the year 20 examination, baseline for this analysis.

Ascertainment of Covariates

Data on age, sex, race, and smoking status were collected using standardized questionnaires. Height and weight were measured by certified technicians from participants wearing light clothing and no shoes and were used to calculate BMI in kg/m^2. Systolic blood pressure (SBP) was measured following standardized protocols (12). After resting for 5 min in the seated position, blood pressure was measured three times at 1-min intervals using an appropriately sized cuff, with the average of the second and third measurements used to determine SBP. SBP was measured at year 20 using a standard automated blood pressure measurement monitor (Omron model HEM907XL) calibrated to the random zero sphygmomanometer that had been used at each earlier examination. Total cholesterol was measured enzymatically, and HDL cholesterol was determined by precipitation with dextran sulfate–magnesium chloride at the University of Washington (12).

CAC

Electron beam computed tomography (CT; Chicago and Oakland field centers at year 20) or multidetector CT scanners (Birmingham and Minneapolis field centers at year 20 and all centers at year 25) were used to assess CAC by obtaining contiguous transverse images from the root of the aorta to the apex of the heart (13). The comparability of electron beam CT and multidetector CT has been demonstrated previously (14). Pregnant women and participants who exceeded the weight restriction for the scanner were ineligible. The CT scanning protocol included a hydroxyapatite calibration phantom to monitor image brightness and noise. A calcium score in Agatston units (15) was calculated for each calcified lesion, and the scores were summed across all lesions within a given artery and across all arteries (left anterior descending, left main, circumflex, and right coronary) to obtain the total calcium score. For the one participant who had coronary artery bypass graft surgery prior to the year 25 examination, only the native coronary arteries were scored for calcification. Three participants had had coronary stents at year 20 and four at year 25; stented areas were not scored, but 100 Agatston units was added to each person with any stents. All scans were read centrally with high interobserver (κ = 0.89) and intraobserver (κ = 0.95) agreement for the presence of CAC (13).

CAC progression was assessed as *1*) incident CAC defined as an increase $>$0 Agatston units among those without CAC at baseline (i.e., from 0 at year 20 to $>$0 Agatston units at year 25), *2*) any CAC progression defined as an increase $>$10 Agatston units (i.e., from 0 at year 20 to $>$10 at year 25 or $>$10 unit increase in CAC score at year 25 among those with CAC at year 20), and *3*) advanced CAC progression defined as a change $>$100 Agatston units between years 20 and 25 (i.e., from 0 at year 20 to $>$100 at year 25 or $>$100 unit increase in CAC score at year 25 among those with CAC at year 20).

Statistical Analyses

The association of HbA_{1c} with CAC progression was evaluated using Poisson regression with robust variance estimation to obtain risk ratio (RR) and 95% CI (16). HbA_{1c} was evaluated as a continuous variable with a 1-unit increase defined as 1% (10.9 mmol/mol). Model 1 was unadjusted, model 2 was adjusted

for sociodemographics (age, sex, race, education, and study field center), and model 3 included additional adjustments for cardiovascular risk factors (SBP, use of antihypertensive medications, total cholesterol, HDL cholesterol, current smoking, and BMI). Model 4 also included adjustment for the presence of baseline CAC for any CAC progression and advanced CAC progression analyses. Effect modification by race was investigated in fully adjusted models using interaction terms.

Secondary analyses were carried out to evaluate the association of HbA_{1c} with CAC progression. First, an alternative definition of CAC progression, defined as a change $\geq$2.5 mm^3 between square root-transformed volumetric scores, was used (17). Second, because individuals with prevalent CAC are more likely to experience CAC progression, the association of HbA_{1c} with the log-transformed quantity of CAC progression was also evaluated among individuals with CAC at the year 20 examination. Lastly, the association of HbA_{1c} with CAC progression was evaluated using HbA_{1c} quartiles to assess possible nonlinear associations. The α-level used for all analyses was 0.05. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Participant characteristics at baseline are presented in Table 1. The mean age of participants was 45.3 years, 40.9% were African American, and 57.3% were female. The mean HbA_{1c} was 5.3%, and 18.4% of participants had baseline CAC at the year 20 examination.

Any CAC progression and advanced CAC progression were more likely to occur among individuals with CAC present at the year 20 examination (Fig. 1). Among participants with CAC at the year 20 examination, 69.7% experienced any CAC progression >10 Agatston units, and 28.5% experienced advanced CAC progression >100 Agatston units during the 5-year follow-up period. In contrast, among participants without CAC at the year 20 examination, 6.5% experienced any CAC progression, and 0.2% experienced advanced CAC progression. Overall, 12.9% of individuals without baseline CAC at the year 20 examination developed incident CAC >0 Agatston units by the year 25 examination.

Table 1—Baseline characteristics of study participants without diabetes, the CARDIA study, 2005–2006

N	2,076
Age (years), mean (SD)	45.3 (3.6)
Race, *n* (%)	
African American	848 (40.9)
White	1,228 (59.1)
Sex, *n* (%)	
Female	1,189 (57.3)
Male	887 (42.7)
Education ≤high school, *n* (%)	475 (22.9)
BMI (kg/m^2), mean (SD)	28.7 (6.1)
Current smoker, *n* (%)	371 (17.9)
SBP (mmHg), mean (SD)	114.6 (14.1)
Use of blood pressure medications, *n* (%)	283 (13.6)
Total cholesterol (mg/dL), mean (SD)	187.2 (34.3)
HDL cholesterol (mg/dL), mean (SD)	55.0 (16.8)
Fasting glucose (mg/dL), mean (SD)	94.4 (9.4)
HbA_{1c}, mean (SD)	
NGSP, %	5.3 (0.4)
IFCC, mmol/mol	34 (4.4)
CAC present at baseline, *n* (%)	383 (18.4)

The unadjusted and adjusted effect estimates for the association of HbA_{1c} with CAC progression are presented in Table 2. HbA_{1c} was associated with incident CAC after adjustment for sociodemographic factors (RR = 1.45; 95% CI 1.02, 2.06), but this association was attenuated after additional adjustment for cardiovascular risk factors (RR = 1.05; 95% CI 0.74, 1.49). Similarly, higher HbA_{1c} was associated with any CAC progression >10 Agatston units after adjustment for age, sex, race, education, and study field center (RR = 1.51; 95% CI 1.16, 1.96), but this association was attenuated in the multivariable model (RR = 1.13; 95% CI 0.87, 1.47). Higher HbA_{1c} was associated with advanced CAC progression >100 Agatston units after adjustment for sociodemographics (RR = 2.42; 95% CI 1.47, 3.99), and this association remained after additional adjustment for cardiovascular risk factors (RR = 1.78; 95% CI 1.08, 2.95) and baseline CAC (RR = 1.75; 95% CI 1.09, 2.83).

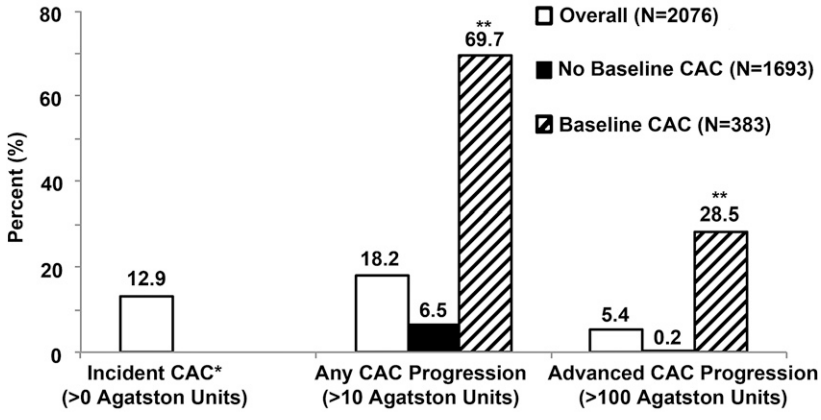

Figure 1—Percentage of participants with CAC progression during the 5-year follow-up period, overall and by baseline CAC presence, in the CARDIA study. *Evaluated only among individuals without CAC at the year 20 examination. **$P < 0.001$ comparing proportion with baseline CAC to no baseline CAC.

Table 2—RR and 95% CI evaluating the association of a 1-unit increase in HbA_{1c} with CAC progression over 5 years among individuals without diabetes in the CARDIA study

Model	RR (95% CI)
Incident CAC* (>0 Agatston units), *n* = 1,693	
Model 1	1.55 (1.12, 2.14)
Model 2	1.45 (1.02, 2.06)
Model 3	1.05 (0.74, 1.49)
Any CAC progression (>10 Agatston units), *n* = 2,076	
Model 1	1.57 (1.24, 1.99)
Model 2	1.51 (1.16, 1.96)
Model 3	1.13 (0.87, 1.47)
Model 4	1.09 (0.87, 1.37)
Advanced CAC progression (>100 Agatston units), *n* = 2,076	
Model 1	2.69 (1.76, 4.13)
Model 2	2.42 (1.47, 3.99)
Model 3	1.78 (1.08, 2.95)
Model 4	1.75 (1.09, 2.83)

One-unit increase in HbA_{1c} = 1% (10.9 mmol/mol). Model 1, unadjusted; model 2, adjusted for age, race, sex, education, and study field center; model 3, adjusted for variables in model 2 plus SBP, antihypertensive medication use (yes/no), current smoking status (yes/no), total cholesterol, HDL cholesterol, and BMI; model 4, adjusted for variables in model 3 plus baseline CAC. *Evaluated only among individuals without CAC at the year 20 examination.

Effect modification by race was evaluated but was not statistically significant for any of the CAC progression measures (interaction *P* values >0.35). Analyses stratified by race are presented in Supplementary Table 1 and show similar associations, although the CIs overlap and lack precision, particularly for advanced CAC progression. For the analysis of HbA_{1c} with CAC progression using the change in CAC volumetric score, 311 (15.0%) participants experienced CAC volume progression ≥2.5 mm^3, but the association of HbA_{1c} with CAC progression was attenuated and not statistically significant after adjustment for demographics, cardiovascular risk factors, and baseline CAC (RR = 1.31; 95% CI 0.97, 1.76). In another analysis focused solely on progression among individuals with CAC at baseline, HbA_{1c} was not associated with an increase in the log-transformed Agatston score (β = 0.44; 95% CI −0.08, 0.96). Additionally, the association of HbA_{1c} with CAC progression was explored using HbA_{1c} quartiles, and the findings were similar to the results for continuous HbA_{1c} when comparing the highest HbA_{1c} quartile with the lowest HbA_{1c} quartile for incident CAC (RR = 1.06; 95% CI 0.72, 1.55), any CAC progression (RR = 1.14; 95% CI 0.85, 1.54), and advanced CAC progression (RR = 2.12; 95% CI 1.08, 4.19).

CONCLUSIONS

In this prospective cohort study of individuals without diabetes, 18.2% of participants experienced CAC progression >10 Agatston units over a 5-year follow-up period, and CAC progression was more common among those individuals with baseline CAC present compared with those without baseline CAC. Higher HbA_{1c} was associated with incident CAC and any CAC progression, but these associations were attenuated and not independent of other cardiovascular risk factors. However, higher HbA_{1c} was associated with advanced CAC progression >100 Agatston units, and this association persisted after adjustment for cardiovascular risk factors.

Prior studies investigated the cross-sectional association of HbA_{1c} with prevalent CAC among individuals without diabetes and reported conflicting results. No association between HbA_{1c} and calcified plaque was reported in a study of middle-aged Korean adults (8). In contrast, another study of middle-aged Korean men and women participating in a health screening program (CAC prevalence = 10.9%) reported higher HbA_{1c} was associated with prevalent CAC (9). In the Multi-Ethnic Study of Atherosclerosis, higher HbA_{1c} was also associated with prevalent CAC (10). However, this association was present for women and not men in that community-based study of older adults (mean age = 63.2 years) that had a high prevalence of CAC (53.5%). The differences in participant characteristics and CAC prevalence may have contributed to the contrasting findings reported for the association of HbA_{1c} with CAC prevalence. Additionally, the prior studies did not evaluate CAC progression as we did in our community-based study of middle-aged adults. In our study, HbA_{1c} was not associated with incident CAC or any CAC progression >10 Agatston units after taking into account other established cardiovascular risk factors, whereas higher HbA_{1c} was independently associated with advanced CAC progression >100 Agatston units.

The physiologic pathway linking HbA_{1c} and cardiovascular disease outcomes is not fully understood. A recent analysis of participants without diabetes from 73 prospective studies reported higher HbA_{1c} was associated with an increased risk of clinical cardiovascular events, although the addition of HbA_{1c} to risk prediction models resulted in marginal improvements in cardiovascular disease risk assessment beyond traditional cardiovascular disease risk factors (18). As an integrated marker of glycemia, HbA_{1c} represents a general process of enhanced posttranslational glycation of many proteins that may relate differently to the various development stages of macrovascular disease for individuals without diabetes. Prior findings from studies of HbA_{1c} and other markers of subclinical atherosclerosis have reported contrasting findings. Cross-sectional studies have reported positive associations of HbA_{1c} with carotid artery intima-media thickness (19–23) and echogenic carotid plaque (24). In contrast, no associations have been reported for HbA_{1c} with echolucent carotid plaque (24) and change in intima-media thickness or new plaque development over 5 years of follow-up (25).

CAC represents a particular advanced stage in the atherosclerotic plaque (26), namely, metabolism incorporating calcium within an existing plaque, so its pathogenesis may differ from other markers of subclinical atherosclerosis. Our study did not find independent associations with incident CAC or any CAC progression >10 Agatston units, but HbA_{1c} was independently associated with advanced CAC progression >100 Agatston units. Because individuals with diabetes experience greater CAC progression than those without diabetes (27), it is

possible that the association observed for those with advanced CAC progression >100 Agatston units was reflective of the development of diabetes. However, HbA_{1c} was not independently associated with any of the CAC progression measures among individuals with diabetes at baseline in our study (data not shown), and HbA_{1c} remained independently associated with advanced CAC progression >100 Agatston units (RR = 1.80; 95% CI 1.06, 3.06) after multivariable adjustment and excluding 102 individuals who developed diabetes during the follow-up. These findings suggest HbA_{1c} may exhibit differential associations with CAC progression measures, indicating a complex association of HbA_{1c} with multiple markers of subclinical atherosclerosis and potentially cardiovascular events.

This study has several potential limitations. HbA_{1c} was not measured until the year 20 examination, so participants who did not attend this examination and participants who did not have CT scans completed at the year 20 and 25 examinations were not included in these analyses. The retention of CARDIA participants is high, but participants who were excluded from this analysis differed from those who were included, and this may have affected our study's findings. Excluded participants were more likely to be younger, African American, and current or former smokers and have higher BMI and higher SBP, while no differences were noted for sex, education, lipids, and medication use when compared with participants included in this analysis. Additionally, HbA_{1c} values may be affected by genetic factors and certain medical conditions such as anemia and liver disease (28,29). Excluding 55 individuals who self-reported a physician diagnosis of anemia or liver disease did not alter findings. HbA_{1c} reflects glycemic control over several months, but only a single baseline measure of HbA_{1c} was used in this analysis, and the association of HbA_{1c} with CAC progression may be better captured with the use of multiple HbA_{1c} measurements. Currently, there are no standard guidelines for the assessment of CAC progression (30), so this study investigated several definitions of CAC progression, and the conclusions were the same using absolute change in Agatston units and change in volumetric score definitions for this relatively young population (ages 38–50 years when CAC was assessed at the year 20 examination). Additionally, although we used multiple absolute and relative definitions of CAC progression, interscan variability may have affected the CAC progression outcomes in our study. Repeat scans were performed at the year 20 examination to assess interscan variability. Interscan variability decreased as the degree of CAC increased, with the mean (SD) for the absolute differences in scans being 56.6 (53.5) for the Agatston score and 1.3 (1.4) for the volumetric score, respectively, for participants with an Agatston score >100 at baseline. The majority of the participants did not have CAC at baseline, and the follow-up period was 5 years, so this study had limited power to assess associations with greater degrees of CAC progression. However, the investigation of CAC during this early stage of middle age is important given the established associations with future cardiovascular events.

In summary, CAC progression was a common occurrence among middle-aged adults without diabetes in this study. Higher HbA_{1c} was associated with CAC progression over 5 years of follow-up, although it was only independently associated with advanced CAC progression >100 Agatston units after taking into account cardiovascular risk factors. This suggests that the pathway linking HbA_{1c} with clinical cardiovascular events among individuals without diabetes may not be evidenced at the earlier stages of subclinical atherosclerosis development. More comprehensive elucidation of the relation of glycemia, subclinical atherosclerosis, and clinical cardiovascular events among individuals without diabetes is warranted.

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Author Contributions. A.P.C. conceptualized the study, designed the analysis, interpreted the data, and drafted the manuscript. M.W.S., M.R.C., J.P.R., and C.M.L. interpreted the data and critically revised the manuscript for important intellectual content. J.J.C., M.D.G., D.R.J., and C.E.L. secured funding, interpreted the data, and critically revised the manuscript for important intellectual content. Y.K. researched the data, performed the statistical analysis, and critically revised the manuscript for important intellectual content. A.P.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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