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ORIGINAL ARTICLE

Glycemic Markers and Subclinical Cardiovascular Disease: The Jackson Heart Study

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BACKGROUND: We investigated the associations of glycemic markers (HbA_{1C} [hemoglobin A_{1C}], fasting plasma glucose, and insulin resistance—homeostasis model assessment of insulin resistance) with subclinical cardiovascular disease (CVD) among blacks.

METHODS: We included 4303 community-dwelling blacks (64% women; mean age, 54.5 years) without prevalent CVD. Subclinical CVD was defined as ≥1 of the following: any coronary artery calcification (CAC), elevated carotid intima-media thickness (cIMT), left ventricular (LV) hypertrophy, LV ejection fraction <50%, and peripheral artery disease (ankle-brachial index, <0.90). Estimates of cross-sectional associations of glycemic markers (fasting plasma glucose, HbA_{1C}, and homeostasis model assessment of insulin resistance) with subclinical CVD measures were adjusted for traditional CVD risk factors.

RESULTS: Each 1% increment in HbA_{1C} was associated with higher odds of CAC, abnormal cIMT, and subclinical CVD (all P <0.001). Adjusted mean values of LV mass (LVM), LVM index, relative wall thickness, CAC, and cIMT were increasingly abnormal with worsening HbA_{1C} categories (all P <0.05). Each 10-mg/dL increase in fasting plasma glucose was associated with higher odds of LV hypertrophy, CAC, abnormal cIMT, and subclinical CVD (all P <0.005). Adjusted mean values of LVM, LVM index, relative wall thickness, CAC, ankle-brachial index, and cIMT were more abnormal across categories of worsening fasting plasma glucose (all P <0.05). Each unit increment in log-transformed homeostasis model assessment of insulin resistance conferred a higher odd of having LV hypertrophy (P<0.01). Across quartiles of homeostasis model assessment of insulin resistance, we observed progressively abnormal adjusted mean values of LVM, LVM index, relative wall thickness, and ankle-brachial index (all P <0.01).

CONCLUSIONS: Among blacks, glycemic markers were differentially associated with various measures of subclinical CVD.

Key Words: blood glucose ■ cardiovascular diseases ■ female ■ glycated hemoglobin A ■ humans ■ insulin resistance

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CLINICAL PERSPECTIVE

We investigated the association of various measures of glucose homeostasis and several indices of subclinical cardiovascular disease, which include measures of cardiac structure/function, coronary artery calcification, carotid intima-media thickness, and peripheral artery disease, in a large sample of blacks in the Jackson Heart Study. Several subclinical cardiovascular disease measures were abnormal among individuals with either prediabetes or diabetes mellitus (versus individuals with a normal glycemia), with particularly strong associations for measures of coronary artery calcification and for an overall measure of subclinical cardiovascular disease. Our findings provide useful information on the extent of cardiovascular disease risk across the glycemic spectrum. First, they confirm that diabetes mellitus is related to worse measures of subclinical cardiovascular disease. Second, they demonstrate that in early stages of dysglycemia, that is, nondiabetic range hyperglycemia (prediabetes), subclinical cardiovascular disease is already present. Consequently, our findings suggest that a combined and concomitant approach to the primary prevention of both type 2 diabetes mellitus and cardiovascular disease would be optimal, compared with individual approaches. However, additional studies are necessary to inform such an approach.

Diabetes mellitus and cardiovascular disease (CVD) are highly prevalent in the United states, more so among blacks than other ethnic/racial groups.[1,2] Glycemic markers, including fasting plasma glucose (FPG) and HbA_{1C} (hemoglobin A_{1C}), have been shown to be associated with incident cardiovascular events and mortality among individuals with and without diabetes mellitus.[3,4] Because the occurrence of clinical CVD events is influenced by factors related to plaque rupture and thrombosis, evaluation of the relation between glycemic markers and subclinical CVD may provide additional insight into the role of hyperglycemia during the early stages of atherosclerosis. However, a limited number of studies have comprehensively assessed the relationship between glycemic markers (HbA_{1C} and FPG) and various subclinical CVD measures (subclinical cardiac remodeling, carotid intima-media thickness [cIMT], ankle-brachial index [ABI], and coronary artery calcification [CAC]) among individuals with and without diabetes mellitus.[5–7] Some studies have suggested a larger influence of FPG on CAC scores among blacks, than in other ethnic/racial groups.[8] Other studies suggest that the relation of HbA_{1C} and CAC score tends to be larger among whites than in Asians, blacks, and Hispanics.[5] However, the proportion of nonwhite individuals was relatively limited in these studies. Furthermore, HbA_{1C} levels tend to be significantly higher in black individuals (with or without diabetes mellitus) than individuals from other ethnic/racial groups at any given blood glucose level.[9] However, limited data exist on whether the association of HbA_{1C} with outcomes, including subclinical outcomes, varies by race/ethnicity and thus may have a differential prognosis significance.[7,10] Thus, the need to investigate whether the relation of HbA_{1C} with subclinical outcomes differs from that of other glycemic markers among blacks. Such an investigation will help clarify whether HbA_{1C} should be used differently among blacks for diabetes mellitus diagnosis or not.

Using the community-based JHS (Jackson Heart Study) cohort, we evaluated the associations of several glycemic markers (FPG, HbA_{1C}, and insulin resistance) with multiple noninvasive measures of subclinical CVD, among black individuals with and without diabetes mellitus.

METHODS

Study Sample

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The JHS recruited 5306 blacks, aged 21 to 94 years, from the Jackson, Mississippi, metropolitan area.[11] The JHS study design and methods have been described elsewhere.[11] The present study included participants who underwent the baseline examination (examination 1) between September 2000 and March 2004. We excluded participants with prevalent clinical CVD (history of myocardial infarction, coronary artery bypass graft, stroke, or heart failure; n=572) and with ABI >1.40 (n=431, given that such individuals frequently have medial arterial calcification and artifactually high ABI measurements[12]). The study protocol was approved by the Institutional Review Board of the University of Mississippi Medical Center, Jackson State University, and Tugaloo College. All the participants provided informed consent.

Markers of Glucose Metabolism

The markers of glycemia were assessed at examination 1. HbA_{1C} was measured using high-performance liquid chromatography (Tosoh 2.2; Tosoh Corporation, Tokyo, Japan). The coefficient of variation for HbA_{1C} assay ranged from 1.4% to 1.9%. A National Glycohemoglobin Standardization Program–certified assay was used to measure HbA_{1C}. FPG was measured using the glucose oxidase method. Glucose assays were run in duplicate; the intra-assay coefficient of variation was <3%. Fasting insulin levels were measured in plasma as total immunoreactive assay with standardization to serum levels for reporting purposes. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: (fasting glucose [mmol/L]×fasting insulin [μU/mL])/22.5.[13]

Diabetes mellitus was defined according to the American Diabetes Association criteria as an FPG ≥126 mg/dL or HbA_{1C}

≥6.5%,[14] self-reported diabetes mellitus or confirmed use of insulin or oral hypoglycemic medications at the index clinical examination, or a self-report of physician-diagnosed diabetes mellitus. Prediabetes was defined as an FPG of 100 to 125 mg/dL or HbA_{1C} of 5.7% to 6.4%.[14]

Subclinical CVD Measures and Score

Cardiac Structure Indices

The outcomes measured included echocardiographic indices obtained at examination 1: left ventricular (LV) mass (LVM), LVM index, relative wall thickness (RWT), LV hypertrophy (LVH), LV ejection fraction (LVEF), and E-wave velocity/A-wave velocity ratio (E/A ratio). Two-dimensional and M-mode echocardiography was performed using a Sonos 4500 cardiac ultrasound machine (Hewlett Packard, Andover, MA). Measurements were performed offline by 4 trained echocardiographers based on American Society of Echocardiography recommendations.[15] LVM was measured in M mode and was calculated using the American Society of Echocardiography–corrected formula: LVM (g)=0.8×1.04 [(LV end-diastolic diameter+interventricular septal wall thickness+posterior wall thickness)^3–(LV end-diastolic diameter)^3]+0.6. LVEF was determined visually. For this analysis (n=4085), LVH was defined as an LVM indexed to height$^{2.7}$ >51 g/ht,[16] and a low ejection fraction was defined as an LVEF <50%. E/A ratio <0.8 or >1.5 was defined as abnormal diastolic function (n=3831).

Coronary Artery Calcium

CAC score was measured 4 years after (at examination 2 in 2005–2008) the assessment of FPG and HbA_{1C}. Computed tomographic imaging of the torso was obtained by multidetector computed tomography (GE Healthcare Lightspeed 16 Pro; Wakeshau, WI). The participants were scanned in the supine position with a 3-sample calcium calibration QCT Phantom (Image Analysis, Columbia, KY) posterior to the spine. Scans were electrocardiographically triggered to the R-R interval, and images were obtained at end diastole during a single breath-hold; CAC was scored according to the Agatston method used in large epidemiological studies.[17] The presence of CAC was defined as having an Agatston score >0. We also categorized CAC into 3 groups: 0, 1 to 100, and >100.[18]

Peripheral Artery Disease

Peripheral artery disease (PAD) was defined based on ABI measurements obtained at examination 1. With the participant in the supine position after 5 minutes of rest, a specially trained and certified nurse used a mercury sphygmomanometer to measure the blood pressure (BP) in each arm and leg. Systolic BP (SBP) of the brachial artery was used for the upper extremities, whereas duplicate SBPs of the posterior tibial artery were used for the 2 lower extremities. The ABI was calculated separately for each leg by taking the higher SBP in each lower extremity and dividing by the highest upper-extremity SBP. The lowest of these 2 leg-specific ABIs was used to classify the ABI score for each participant.[19] PAD was defined as an ABI <0.90. A total of 3754 individuals had data available on ABI.

Carotid Intima-Media Thickness

cIMT measurements were obtained at examination 1 using a Hewlett Packard Sonos 4500 ultrasound imaging device at the left and right carotid arteries at the common, bifurcation, and internal sites. Three circumferential views were assessed at the common and bifurcation segments (anterior, lateral, and posterior). A single view was obtained at the internal segment. For the analysis, we used the estimate based on the average right and left common carotid far wall and referred to it as cIMT. We examined cIMT as continuous outcomes.[20] A total of 4057 individuals had available cIMT measurements.

Subclinical CVD

We defined a subclinical CVD index that has been validated previously,[21] which consists of at least 1 of the following: LVH (by echocardiography), LV systolic dysfunction (by echocardiography—LVEF <50%), presence of CAC, presence of carotid atherosclerotic disease, and a reduced ABI. We used the following to define the components of the subclinical CVD score: presence of CAC defined as having an Agatston score >0, PAD defined as ABI <0.9, LVH defined as an LVM indexed to height$^{2.7}$ >51 g/ht, low ejection fraction defined as an LVEF <50%, and the presence of carotid disease defined as a standardized cIMT that meets or exceeds the sex-specific 80th percentiles in the sample or an extreme increase in common cIMT ≥1 mm.

Covariates

Covariates, including demographic and behavioral characteristics, as well as medical history and medication use, were assessed by standardized questionnaires, physical examination, and laboratory tests. Methods of risk factor ascertainment in JHS have been reported elsewhere.[11]

Current smokers were defined as those who reported having smoked ≥1 cigarette per day regularly during the year preceding the examination. Height and weight were measured, and body mass index was calculated (kg/m^2). BP was measured twice in the left arm of the seated subject with a mercury column sphygmomanometer. The average of the 2 readings was used as the examination BP, and hypertension was defined as SBP ≥140 mm Hg or diastolic BP ≥90 mm Hg, or self-reported antihypertensive medication use. Serum creatinine was measured using the rate Jaffe reaction, and the kidney function was assessed using the estimated glomerular filtration rate calculated by the CKD-EPI study (Chronic Kidney Disease Epidemiology Collaboration) equation.[22] Plasma total cholesterol, HDL (high-density lipoprotein) cholesterol, and triglyceride concentrations were measured using standard enzymatic methods, on a Vitros 950 or 250, Ortho-Clinical Diagnostics analyzer (Raritan, NJ) in accordance with the College of American Pathologists Proficiency Testing Program.[23] LDL (low-density lipoprotein) cholesterol was calculated using the Friedewald equation.[24] Information on personal medical and family history, medication use, physical activity, alcohol use (within the past 12 months), and current smoking (smoking at the time of the interview) was obtained using standardized questionnaires during the baseline examination.

Statistical Analysis

We classified participants into clinically relevant categories of HbA_{1C} (<5.7%; 5.7%–6.4%, and ≥6.5%) and compared differences in baseline characteristics of participants' variables across HbA_{1C} groups, using ANOVA (for continuous variables) or the χ^2 test (for categorical variables). Skewed variables were appropriately transformed. We also assessed the baseline characteristics of participants by categories of glucose intolerance (defined either by FPG alone or FPG and HbA_{1C} concomitantly) and by quartiles of HOMA-IR.

We used regression models to assess the association of the glycemic markers (FPG, HbA_{1C}, and HOMA-IR, both as continuous and categorical variables) with subclinical CVD measures. The relation of HOMA-IR and subclinical CVD was assessed in subjects without diabetes mellitus because of the potential confounding by diabetes mellitus treatment and complications. We used ANCOVA to evaluate the association of each marker of glycemia with each subclinical CVD measure on a continuous scale; least square means were estimated across relevant categories for each subclinical measure. For the CAC scores, given that these are right skewed, and 54.8% had CAC scores of 0, we added 1 to the CAC score for each participant, and natural log-transformed the resulting variable, thus our outcome was ln(CAC+1) as an outcome. Because the distribution of cIMT was also right skewed, the values were log-transformed.

We evaluated the association of each glycemic marker and the categories of some of the subclinical measures (CAC, PAD, and cIMT) using clinically known cut points (thresholds validated against outcome events described in the literature[25–27]) and logistic regression models to estimate the odds ratios (ORs; 95% CI) of subclinical disease by glycemic marker. Multinomial logistic regression models were used to assess the association with CAC score categorized as 0 (reference), 1 to 100, and >100. For each participant, we constructed an overall presence of subclinical disease variable based on the presence of any of the following CAC, LVH by ECG or echocardiography, LV systolic dysfunction by echocardiography, carotid ultrasound abnormality, and PAD by ABI—an approach that has been used previously.[21] If ≥1 of these subclinical CVD measures were abnormal, this defined the overall presence of subclinical CVD. For each outcome, identical covariates in models were used to facilitate comparisons. The adjustment variables included age, sex, lifestyle factors (smoking and alcohol use), and biological or clinical risk factors (body mass index, ratio of total cholesterol to HDL cholesterol, SBP, use of antihypertensive medications, use of statins, and estimated glomerular filtration rate). We conducted a sensitivity analysis restricting our sample to those without diabetes mellitus.

Two-sided *P* values of <0.05 were considered statistically significant. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Characteristics of the Study Sample

Table 1 summarizes the baseline characteristics of participants by categories of HbA_{1C}. Compared with the lowest HbA_{1C} category, individuals with higher HbA_{1C} ranges were older, more frequently women, had higher FPG levels and a lower renal function, and were more likely to have obesity, hypertension, and an atherogenic lipid profile. The distributions of the characteristics of participants were roughly similar across levels of worsening glycemia using samples defined by categories

Table 1. Characteristics of Jackson Heart Study Participants by Categories of HbA_{1C}

Characteristics	HbA_{1C} Categories			
	<5.7% (n=2083)	5.7%–6.4% (n=1387)	≥6.5% (n=669)	*P* Value
Age, y	51.0 (13.2)	57.6 (11.7)	59.2 (10.8)	<0.0001
Women, n (%)	1338 (64.2)	872 (62.9)	449 (67.1)	0.170
Smoking, n (%)	291 (14.2)	172 (12.6)	75 (11.4)	0.200
BMI, kg/m²	30.1 (7.0)	32.3 (7.3)	34.4 (6.9)	<0.0001
SBP, mm Hg	124.4 (16.0)	129.2 (16.8)	131.9 (17.5)	<0.0001
Diastolic BP, mm Hg	76.0 (8.5)	76.2 (8.8)	75.1 (8.6)	0.013
Total cholesterol, mg/dL	196.8 (38.7)	205.6 (40.7)	201.2 (43.5)	<0.0001
LDL cholesterol, mg/dL	124.6 (35.5)	132.5 (37.6)	125.6 (37.8)	<0.0001
HDL cholesterol, mg/dL	53.8 (15.3)	51.2 (13.9)	49.1 (13.5)	<0.0001
Ratio of total cholesterol to HDL cholesterol	3.9 (1.3)	4.3 (1.4)	4.4 (1.4)	<0.0001
Log-triglycerides, mg/dL	4.4 (0.5)	4.6 (0.5)	4.8 (0.6)	<0.0001
FPG, mg/dL	88.1 (8.8)	94.8 (10.9)	148.1 (61.0)	<0.0001
eGFR, mL/min per 1.73 m²	98.7 (20.4)	92.0 (19.5)	91.9 (24.5)	<0.0001
Obesity (BMI ≥30 kg/m²), n (%)	863 (41.5)	779 (56.2)	475 (71.0)	<0.0001
Hypertension, n (%)	852 (40.9)	834 (60.1)	524 (78.3)	<0.0001
Use of statins, n (%)	90 (4.7)	150 (11.6)	138 (22.5)	<0.0001
Antihypertensive medications, n (%)	695 (36.0)	690 (53.2)	454 (74.2)	<0.0001

Values are reported as mean (SD) for continuous traits and n (%) for dichotomous traits. BMI indicates body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA_{1C}, hemoglobin A_{1C}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and SBP, systolic blood pressure.

of FPG alone, FPG and HbA_{1C}, and HOMA-IR (Tables I through III in the Data Supplement).

Among the included participants, 41.4% had a normal glycemia, 33.8% had prediabetes, and 19.8% had diabetes mellitus, as defined by both HbA_{1C} and FPG. The prevalence of abnormalities in the markers of subclinical CVD across the categories of glycemic markers is shown in Figure 1 and Table IV in the Data Supplement. The burden of subclinical CVD varied in its distribution; the number of abnormal subclinical disease measures across participants was as follows: 0 (n=986), 1 (n=772), 2 (n=274), 3 (n=54), and 4 (n=5). Using a dichotomous variable that captures the overall burden of subclinical disease (no abnormal subclinical CVD versus ≥1 abnormal subclinical CVD measure), we described the burden of subclinical CVD across glycemic categories, as shown in Figure 2.

HbA_{1C} and Subclinical CVD

Table V in the Data Supplement and Table 2 display the unadjusted and adjusted means of subclinical CVD outcomes (evaluated as continuous outcomes) across clinically relevant HbA_{1C} categories, respectively. Across categories of worsening HbA_{1C} levels, we observed progressively abnormal levels of LVM, LVM index, RWT, E/A ratio, CAC, and cIMT (All *P* trend <0.05).

Table 3 shows the association of HbA_{1C} (as a continuous variable) and each marker of subclinical CVD (as categorical outcome measures). After adjustment for traditional CVD risk factors, each 1% change in HbA_{1C} was associated with higher odds of having CAC (OR, 1.34; 95% CI, 1.20–1.49), carotid atherosclerosis (OR, 1.18; 95% CI, 1.09–1.27), and the overall presence of subclinical CVD (OR, 1.33; 95% CI, 1.17–1.50) and inversely associated with an abnormal E/A ratio (*P*=0.03). We observed no association of HbA_{1C} with LV systolic dysfunction (LVEF<50), LVH, and PAD. In a restricted analysis excluding participants with diabetes mellitus, only LVH showed a significant association with each 1% increase in HbA_{1C} (OR, 1.36; 95% CI, 1.14–1.61).

The odds of having a subclinical CVD abnormality for an HbA_{1C} ≥6.5% (versus HbA_{1C} <5.7%) was significant for the following outcomes (Table 4): any CAC (OR, 2.32; 95% CI, 1.67–3.24), CAC >100 (OR, 3.01; 95% CI, 2.03–4.48), cIMT (OR, 1.82; 95% CI, 1.39–2.39), and overall subclinical CVD (OR, 2.33; 95% CI, 1.59–3.41). A significant odds was associated with an HbA_{1C} of 5.7% to 6.4% (versus in HbA_{1C} <5.7%) for cIMT (OR, 1.45; 95% CI, 1.16–1.80) and for overall subclinical CVD (OR, 1.37; 95% CI, 1.08–1.75).

FPG and Subclinical CVD

Table V in the Data Supplement and Table 2 show the unadjusted and adjusted mean of continuous measures of subclinical CVD across of clinically relevant FPG categories, respectively. Across the categories of worsening FPG levels, we observed progressively abnormal adjusted mean values of LVM, LVM index, RWT, E/A ratio, CAC, ABI, and cIMT (All *P* trend <0.01).

Table 3 shows the association of FPG (as a continuous marker) and each marker of subclinical CVD (as categorical outcome measures). After adjusting for traditional CVD risk factors, each 10 mg/dL change in FPG was associated with higher odds of having LVH (OR, 1.04; 95% CI, 1.01–1.08), CAC (OR, 1.06; 95%

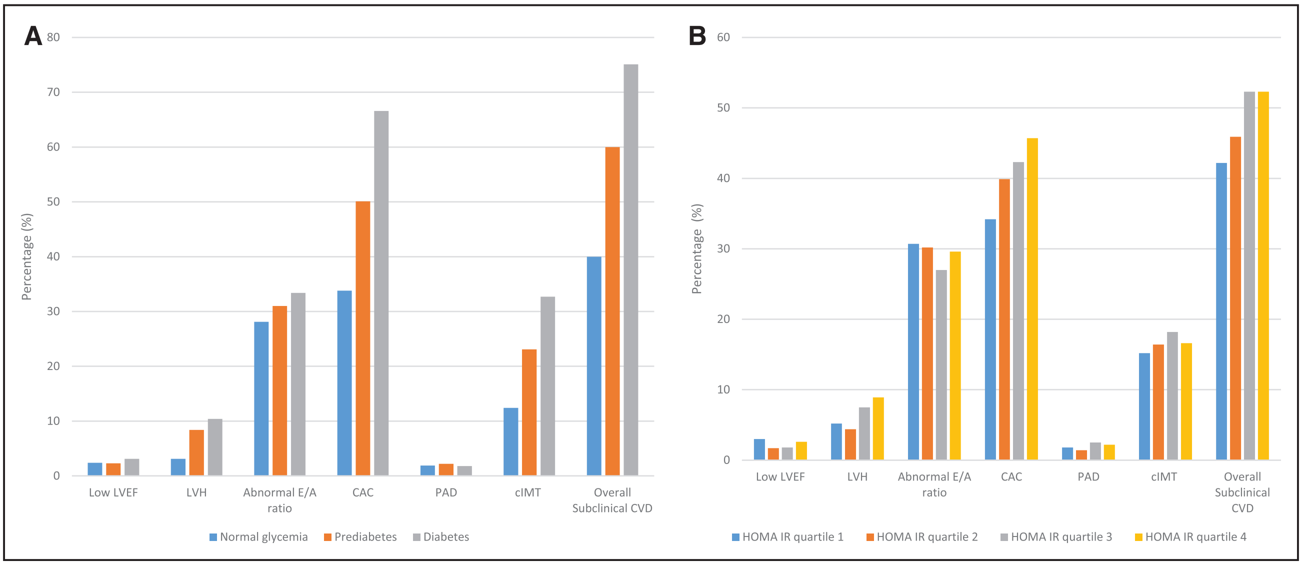

Figure 1. Prevalence of abnormalities in the markers of subclinical cardiovascular disease (CVD) across the categories of glycemic markers.
A, Significant differences across glycemic spectrum (all *P* <0.005) except for left ventricular ejection fraction (LVEF) and peripheral artery disease (PAD). **B**, Significant differences across insulin resistance levels for left ventricular hypertrophy (LVH), coronary artery calcification (CAC), and overall subclinical CVD (all *P* <0.005). cIMT indicates carotid intima-media thickness; E/A ratio, the ratio of the early (E) to late (A) ventricular filling velocities; and HOMA-IR, homeostasis model assessment of insulin resistance.

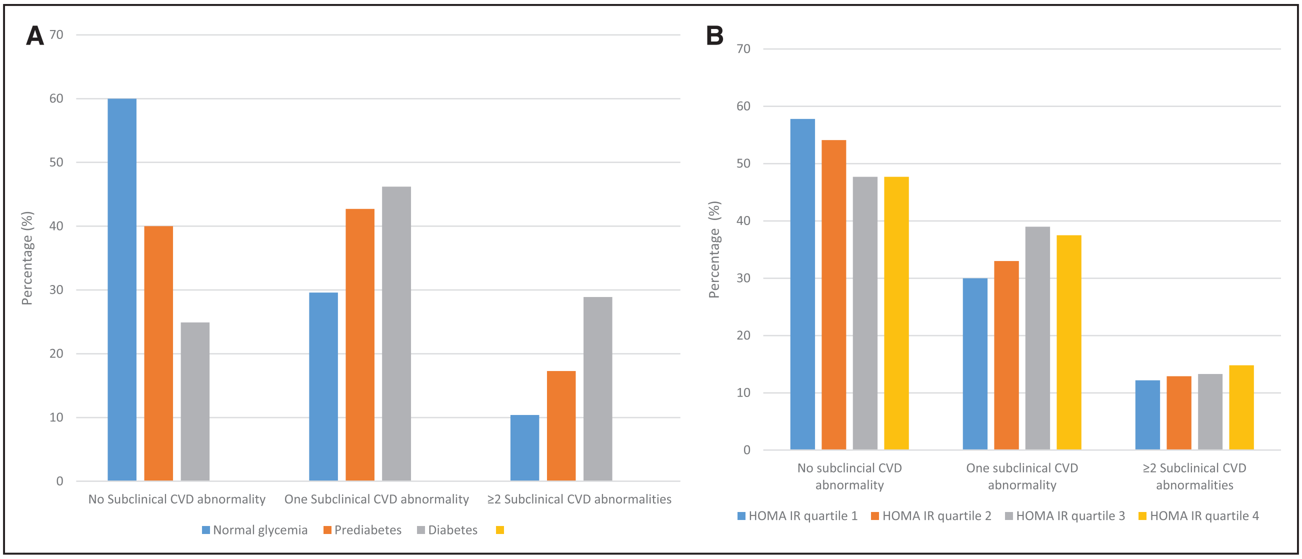

Figure 2. Distribution of the burden of subclinical cardiovascular disease (CVD) by glycemic status.
A and **B**, Significant differences across glycemic spectrum and insulin resistance levels (all *P* <0.05). HOMA-IR indicates homeostasis model assessment of insulin resistance.

CI, 1.02–1.10), carotid atherosclerosis (OR, 1.04; 95% CI, 1.02–1.07), and overall presence of subclinical CVD (OR, 1.07; 95% CI, 1.02–1.12). There was no association of FPG with LV systolic dysfunction (LVEF<50), abnormal E/A ratio, and PAD. In an analysis excluding participants with diabetes mellitus, only LVH showed a significant association with each 10 mg/dL increase in FPG (OR, 1.54; 95% CI, 1.06–2.25).

The odds of having a subclinical CVD abnormality for a FPG ≥126 mg/dL (versus FPG <100 mg/dL) was significant for the following outcomes (Table 4): any CAC (OR, 1.84; 95% CI, 1.23–2.75), CAC >100 (OR, 2.55; 95% CI, 1.55–4.09), cIMT (OR, 1.69; 95% CI, 1.24–2.31), and overall subclinical CVD (OR, 1.90; 95% CI, 1.18–3.05). Compared with FPG <100 m g/dL, a significant odds was associated with an FPG of 100 to 125 mg/dL (versus FPG <100 mg/dL) for LVH (OR, 1.59; 95% CI, 1.14–2.21), any CAC (OR, 1.41; 95% CI, 1.07–1.85), and CAC >100 (OR, 1.49; 95% CI, 1.07–2.08).

Table 2. Adjusted Means for Continuous Measures of Subclinical Cardiovascular Disease by Categories of Glycemic Markers—the Jackson Heart Study

	Categories of HbA_{1c}, %				Categories of FPG, mg/dL				HbA_{1c} (%) and FPG (mg/dL) Categories			
	<5.7%	5.7%–6.4%	≥6.5%	*P* Value	<100 mg/dL	100–125 mg/dL	≥126 mg/dL	*P* Value	Normal Glycemia	Prediabetes	Diabetes Mellitus	*P* Value
EF	61.82 (0.41)	61.84 (0.43)	62.20 (0.496)	0.592	61.63 (0.40)	62.63 (0.48)	62.19 (0.57)	0.009	61.55 (0.42)	61.98 (0.43)	62.28 (0.489)	0.097
LVM, g	147.32 (2.81)	153.03 (2.93)	156.62 (3.395)	<0.001	147.90 (2.72)	160.92 (3.31)	157.71 (3.90)	<0.001	146.97 (2.85)	152.70 (2.92)	157.26 (3.29)	<0.001
LVM index, g/m²	35.32 (0.65)	36.45 (0.68)	37.10 (0.784)	<0.001	35.39 (0.63)	38.22 (0.76)	37.41 (0.90)	<0.001	35.17 (0.66)	36.41 (0.67)	37.45 (0.76)	<0.001
RWT	0.36 (0.004)	0.36 (0.004)	0.37 (0.005)	0.035	0.36 (0.004)	0.37 (0.005)	0.38 (0.006)	0.001	0.36 (0.004)	0.36 (0.004)	0.37 (0.005)	0.039
E/A ratio	1.11 (0.02)	1.08 (0.02)	1.04 (0.022)	<0.001	1.10 (0.02)	1.01 (0.02)	1.01 (0.03)	<0.001	1.12 (0.02)	1.07 (0.02)	1.06 (0.021)	<0.001
Log(CAC+1)	4.66 (0.21)	4.73 (0.21)	5.07 (0.233)	0.043	4.70 (0.20)	4.70 (0.23)	5.24 (0.27)	0.028	4.68 (0.21)	4.63 (0.21)	5.12 (0.226)	0.003
ABI	1.16 (0.008)	1.18 (0.008)	1.17 (0.009)	0.026	1.16 (0.007)	1.18 (0.009)	1.17 (0.01)	0.013	1.16 (0.008)	1.18 (0.008)	1.17 (0.009)	<0.001
Log-cIMT	−0.35 (0.01)	−0.32 (0.01)	−0.31 (0.012)	<0.001	−0.34 (0.01)	−0.33 (0.01)	−0.31 (0.02)	0.021	−0.35 (0.01)	−0.33 (0.01)	−0.31 (0.013)	<0.001

Values are adjusted means. Adjustment variables include age, sex, smoking, alcohol use, ratio of total cholesterol to HDL cholesterol, SBP, use of antihypertensive, use of statins, and eGFR. ABI indicates ankle-brachial index; CAC, coronary artery calcification; cIMT, carotid intima-media thickness; E/A ratio, ratio of the early (E) to late (A) ventricular filling velocities; EF, ejection fraction; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA_{1C}, hemoglobin A_{1C}; HDL, high-density lipoprotein; LVM, left ventricular mass; RWT, relative wall thickness; and SBP, systolic blood pressure.

Table 3. Adjusted ORs for Categorical Measures of Subclinical CVD by Increments in Glycemic Markers—the Jackson Heart Study

	ORs (95% CI)					
	HbA_{1C}		FPG		Log(HOMA-IR)	
	n=4139		n=3960		n=3257	
	Per 1% Increase	*P* Value	Per 10-mg/dL Increase	*P* Value	Per Unit Increase	*P* Value
LVEF <50 %	1.08 (0.89–1.32)	0.414	1.00 (0.93–1.08)	0.944	1.03 (0.64–1.63)	0.893
LVH	1.08 (0.97–1.21)	0.175	1.04 (1.01–1.08)	0.020	1.87 (1.37–2.56)	<0.001
Abnormal E/A ratio	0.92 (08.5–099)	0.031	0.98 (0.95–1.01)	0.133	0.91 (0.71–1.07)	0.239
Any CAC	1.34 (1.20–1.49)	<0.001	1.06 (1.02–1.10)	0.003	1.09 (0.88–1.36)	0.423
CAC 1–100	1.26 (1.11–1.42)	<0.001	1.04 (0.99–1.09)	0.090	1.14 (0.89–1.45)	0.308
CAC>100	1.47 (1.30–1.68)	<0.001	1.09 (1.04–1.14)	<0.001	1.03 (0.76–1.39)	0.856
Presence of PAD	0.84 (0.63–1.13)	0.247	0.94 (0.84–1.05)	0.274	1.19 (0.67–2.12)	0.543
Abnormal cIMT	1.18 (1.09–1.27)	<0.001	1.04 (1.02–1.07)	0.001	0.89 (0.72–1.10)	0.273
Overall presence of subclinical CVD	1.33 (1.17–1.50)	<0.001	1.07 (1.02–1.12)	0.005	1.09 (0.86–1.37)	0.478

Values are ORs (95% CI) and *P* values. Each OR captures the risk associated with the change in subclinical disease per 1-unit increase in the SD of each marker. The ORs are adjusted for age, sex, body mass index, smoking, alcohol use, ratio of total cholesterol to HDL cholesterol, SBP, use of antihypertensive, use of statins, and eGFR. CAC indicates coronary artery calcification; cIMT, carotid intima-media thickness; CVD, cardiovascular disease; E/A ratio, ratio of the early (E) to late (A) ventricular filling velocities; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA_{1C}, hemoglobin A_{1C}; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; OR, odds ratio; PAD, peripheral artery disease; and SBP, systolic blood pressure.

Glucose Tolerance Defined by Glycosylated Hemoglobin and Fasting Plasma, and Subclinical CVD

Table 2 describes the adjusted association of glycemic categories, defined by both HbA_{1C} and FPG, with subclinical CVD outcomes (evaluated as continuous outcomes). Across increasing levels of impaired glucose regulation, we observed progressively abnormal levels (expressed as mean values adjusted for traditional CVD risk factors) of the following subclinical measures: LVM, LVM index, RWT, E/A ratio, CAC, ABI, and cIMT (All *P* trend <0.05).

The odds of having a subclinical CVD abnormality among those with diabetes mellitus (versus normoglycemia) was significant for a number of outcomes (Table 4); these include any CAC (OR, 2.48; 95% CI, 1.82–3.39), CAC >100 (OR, 3.32; 95% CI, 2.28–4.84), cIMT (OR, 1.77; 95% CI, 1.36–2.30), and overall subclinical CVD (OR, 2.62; 95% CI, 1.83–3.74). Compared with those with normoglycemia, a significant odds was associated with prediabetes for cIMT (OR, 1.38; 95% CI, 1.10–1.78).

Insulin Resistance (Defined by HOMA-IR) and Subclinical CVD

Table V in the Data Supplement and Table 5 describe the unadjusted and risk factor–adjusted mean values of subclinical CVD outcomes (continuous measures) across levels of HOMA-IR (expressed in quartiles), respectively. Across increasing quartiles of HOMA-IR, we observed progressively abnormal levels of LVM, LVM index, RWT, E/A ratio, and ABI (All *P* trend <0.05).

Table 3 shows the association of HOMA-IR (as a continuous marker) and each marker of subclinical CVD (as categorical outcome measures), accounting for traditional CVD risk factors. Each unit change in log-transformed HOMA-IR was positively associated with a higher odds of having LVH (OR, 1.87; 95% CI, 1.37–2.56). Log-transformed HOMA-IR was not associated with LV systolic dysfunction (LVEF<50), abnormal E/A ratio, presence of CAC, carotid atherosclerosis and PAD, and overall presence of subclinical CVD.

The odds of having a subclinical CVD abnormality for the higher quartile of HOMA-IR (versus the lowest quartile) was significant for LVH (OR, 1.98; 95% CI, 1.21–3.21).

DISCUSSION

This study evaluated the associations of several glycemic markers, representing key biological pathways, with subclinical CVD in a community-based sample of blacks. We made several observations. First, increasing levels of HbA_{1C} and FPG were individually and collectively associated with subclinical CVD, with stronger estimates observed with changes in HbA_{1C} as compared with FPG levels. Second, the extent of the association of insulin resistance with the overall presence of subclinical CVD was somewhat different compared with that of HbA_{1C} or FPG, with the latter measures exhibiting a stronger association. Third, the association of glycemic markers with subclinical measures was not homogenous across vascular territories (coronary, carotid, and peripheral arteries). Indeed, HOMA-IR only conferred higher odds of having

Table 4. Adjusted ORs for Categorical Measures of Subclinical CVD by Increments in Glycemic Markers—the Jackson Heart Study

ORs (95% CI)	HbA1C (n=4139)			FPG (n=3960)			HbA1C and FPG (n=4250)			HOMA-IR (n=3257)			
	<5.7%	5.7%–6.4%	≥6.5%	<100 mg/dL	100–125 mg/dL	≥126 mg/dL	NGT	Prediabetes	Diabetes Mellitus	Q1	Q2	Q3	Q4
LVEF<50 %	Ref	1.30 (0.89–2.58)	1.03 (0.50–2.14)	Ref	0.79 (0.41–1.52)	1.05 (0.46–2.38)	Ref	1.08 (0.62–1.77)	1.04 (0.54–2.04)	Ref	0.50 (0.23–1.08)	0.76 (0.37–1.56)	1.00 (0.50–2.01)
LVH	Ref	1.23 (0.90–1.69)	1.00 (0.66–1.52)	Ref	1.59 (1.14–2.21)	1.37 (0.86–2.18)	Ref	1.32 (0.95–1.83)	1.18 (0.80–1.75)	Ref	0.89 (0.52–1.51)	1.59 (0.98–2.59)	1.98 (1.21–3.21)
Abnormal E/A ratio	Ref	0.96 (0.80–1.14)	0.85 (0.66–1.14)	Ref	0.99 (0.81–1.23)	0.90 (0.67–1.21)	Ref	0.97 (0.81–1.16)	0.94 (0.75–1.18)	Ref	0.97 (0.66–1.07)	0.84 (0.66–1.07)	0.99 (0.77–1.27)
Any CAC	Ref	1.14 (0.91–1.44)	2.32 (1.67–3.24)	Ref	1.41 (1.07–1.85)	1.84 (1.23–2.75)	Ref	1.16 (0.92–1.46)	2.48 (1.82–3.39)	Ref	1.10 (0.80–1.67)	1.20 (0.87–167)	1.35 (0.96–1.89)
CAC 1–100	Ref	1.13 (0.87–1.47)	1.95 (1.33–2.84)	Ref	1.36 (1.00–1.85)	1.42 (0.88–2.29)	Ref	1.21 (0.93–1.57)	2.00 (1.40–2.86)	Ref	1.04 (0.72–1.50)	1.17 (0.76–1.79)	1.17 (1.10–1.14)
CAC>100	Ref	1.18 (0.88–1.50)	3.01 (2.03–4.48)	Ref	1.49 (1.07–2.08)	2.55 (1.59–4.09)	Ref	1.11 (0.82–1.51)	3.32 (2.28–4.84)	Ref	1.20 (0.77–1.88)	1.26 (0.80–1.98)	1.32 (0.83–2.12)
Presence of PAD	Ref	1.09 (0.63–1.91)	0.61 (0.26–1.46)	Ref	0.89 (0.47–1.68)	0.82 (0.31–2.16)	Ref	0.75 (0.41–1.34)	0.85 (0.43–1.70)	Ref	0.68 (0.27–1.69)	1.25 (0.55–2.87)	1.25 (0.52–2.98)
Abnormal cIMT	Ref	1.45 (1.16–1.80)	1.82 (1.39–2.39)	Ref	0.95 (0.74–1.21)	1.69 (1.24–2.31)	Ref	1.38 (1.10–1.73)	1.77 (1.36–2.30)	Ref	0.91 (0.66–1.26)	1.00 (0.72–1.39)	0.85 (0.61–1.20)
Overall presence of subclinical CVD	Ref	1.37 (1.08–1.75)	2.33 (1.59–3.41)	Ref	1.15 (0.80–1.56)	1.90 (1.18–3.05)	Ref	1.03 (1.02–1.66)	2.62 (1.83–3.74)	Ref	0.92 (0.65–1.30)	1.40 (0.99–1.99)	1.15 (0.80–1.64)

Values are ORs (95% CI) and *P* values. The ORs are adjusted for age, sex, body mass index, smoking, alcohol use, ratio of total cholesterol to HDL cholesterol, SBP, use of antihypertensive, use of statins, and eGFR. CAC indicates coronary artery calcification; cIMT, carotid intima-media thickness; CVD, cardiovascular disease; E/A ratio, ratio of the early (E) to late (A) ventricular filling velocities; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA_{1C}, hemoglobin A_{1C}; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NGT, normal glucose tolerance; OR, odds ratio; PAD, peripheral artery disease; Ref, Reference; and SBP, systolic blood pressure.

LVH, whereas HbA_{1C} was associated with higher odds of CAC and abnormal cIMT, and FPG was associated with higher odds of LVH, CAC, and abnormal cIMT.

Our observations provide additional insights into the high burden of subclinical disease related to impaired glucose regulation states, which confer a high risk of overt CVD. Several studies have reported on the association of a single glycemic marker and a higher prevalence of subclinical CVD. Some studies have focused on HbA_{1C}, showing that higher levels of HbA_{1C} are positively associated with CAC,[5,6,28] cIMT,[5,28–31] cardiac structure/function indices,[32] and PAD.[33] Other studies showed a positive association of FPG with CAC,[8,34] cIMT,[5,28–30] and cardiac structure/function indices.[7,35] Other studies also investigated the relation of HOMA-IR with cIMT,[36] CAC,[36–38] and cardiac structure/function indices,[35,36] indicating a positive association. Our observations confirm these prior findings and validate the association between glycemic markers and the overall presence of subclinical CVD, which can be considered as a reasonable target for public health efforts. Our study expands on prior studies, which included a limited number of participants of African descent,[5,32,36,38] by focusing on blacks and including a vast array of glycemic markers concomitantly and multiple measures of atherosclerosis arising in different vascular beds (coronary, carotid, and peripheral arteries). Our study suggests that not only diabetes mellitus but also nondiabetic range hyperglycemia is associated with subclinical CVD. This points to the importance of diabetes mellitus prevention to limit CVD. Consequently, one could reasonably envisage a concomitant prevention of diabetes mellitus and CVD. Indeed, prediabetes has been shown to be associated with cardiovascular events.[39] Prevention could be achieved through lifestyle modification, the effect of which prevents diabetes mellitus progression and affect CVD outcomes.[40,41] Pharmacotherapy is also a consideration, as some of the medications indicated for diabetes mellitus prevention have been associated with a reduction in the incidence of cardiovascular events, including, for example, pioglitazone[42] and liraglutide.[43] Hence, it would be logical to conceive of a joint strategy for concomitant prevention of diabetes mellitus and CVD—an approach that is likely to be cost saving compared with individual approaches to preventing each of these conditions. Such a joint approach may be more appropriate for blacks who are disproportionally affected by both diabetes mellitus and CVD compared with other racial/ethnic groups in the United States.[1,2] Our study also suggests that although HbA_{1C} may differ by racial/ethnic groups, its prognostic value among blacks with regard to subclinical outcomes does not fundamentally differ from that of FPG.

We showed that the association of subclinical CVD disease with several biomarkers, which may represent distinct biological pathways. FPG, HbA_{1C}, and HOMA-IR may not capture the same biological phenomenon that

Table 5. Association of HOMA-IR and Measures of Subclinical Cardiovascular Disease in the Jackson Heart Study

	HOMA -IR				
	Q1	Q2	Q3	Q4	*P* Value
EF, %	61.32 (0.481)	61.84 (0.489)	62.20 (0.488)	62.17 (0.498)	0.089
LVM, g	141.57 (3.414)	145.39 (3.474)	153.71 (3.469)	154.35 (3.538)	<0.001
LVM index, g/m^2	33.79 (0.776)	34.68 (0.790)	36.58 (0.789)	36.80 (0.805)	<0.001
RWT	0.35 (0.005)	0.36 (0.005)	0.36 (0.005)	0.36 (0.005)	0.031
E/A ratio	1.16 (0.022)	1.13 (0.022)	1.09 (0.022)	1.08 (0.022)	<0.001
Log(CAC+1)	4.69 (0.264)	4.67 (0.265)	4.67 (0.257)	4.69 (0.266)	0.999
ABI	1.16 (0.009)	1.17 (0.009)	1.18 (0.009)	1.19 (0.009)	<0.001
Log-cIMT	−0.35 (0.012)	−0.36 (0.013)	−0.36 (0.013)	−0.35 (0.013)	0.960

Values are adjusted means values. Adjustment variables include age, sex, smoking, alcohol use, ratio of total cholesterol to HDL cholesterol, SBP, use of antihypertensive, use of statins, and eGFR. ABI indicates ankle-brachial index; CAC, coronary artery calcification; cIMT, carotid intima-media thickness; E/A ratio, ratio of the early (E) to late (A) ventricular filling velocities; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LVM, left ventricular mass; RWT, relative wall thickness; and SBP, systolic blood pressure.

contributes to the occurrence of atherosclerosis. The potential pathways through which hyperglycemia induces atherosclerosis include glucose-induced production of reactive oxygen species with consequential epigenetic changes, activation of the aldose reductase/polyol pathway, and advanced glycation end-product–mediated proatherogenic effects (through activation of the protein kinase C pathway or action on myelopoiesis).[44] In addition to the effects of glucose, insulin resistance (an important component of glucose dysregulation) may have direct proatherogenic effect, for example, through the reduced ability of insulin to activate Akt—a pathway that is antiatherosclerotic.[44] The differential effects of glycemic markers in various vascular beds suggest potential pleiotropic effects. The biological significance of the differential association of glycemic markers and individual subclinical disease measures remains to be determined. Future studies are needed to evaluate these differences.

The strengths of this study include a well-characterized, large, community-based sample of blacks without prevalent CVD, the availability of several glycemic markers, and a comprehensive set of validated subclinical disease measures reflecting the atherosclerotic burden across the cardiovascular system, which were also combined into a composite measure of subclinical CVD to maximize statistical power.

Some limitations should be acknowledged. CAC measurements were made at a follow-up visit 4 years after the measurement of glycemic markers, and not all participants had subclinical CVD measurements available. The glycemic and subclinical disease measures were assessed at a single examination. Such single-occasion measurements are prone to regression dilution bias, and we may have underestimated the true strength of the associations. The cross-sectional nature of our investigation also limits our ability to establish temporality and thus make any causal inference. While we investigated each measure as a continuous variable to decrease the chance of type 2 error, the results should, however, be interpreted within the context of the 95% CIs, which suggest that any missed association would likely be modest, at best. All the participants were blacks in Jackson, Mississippi; thus, results are not generalizable to other populations. Furthermore, we cannot make direct inference on the prognostic value of HbA_{1C} in racial/ethnic groups other than blacks. We did not explore the relative prognostic significance of the subclinical disease measures. To avoid overfitting of the multivariable models, we adjusted only for a smaller set of standard CVD risk factors, not including physical activity or dietary intake. Last, exclusion of individuals because of nonavailable subclinical disease measures is an unavoidable limitation of large epidemiological studies, associated with the requirement for availability of data for the overall presence of subclinical CVD measure.

In conclusion, in a community-based sample of black adults, we showed that increasing levels of several glycemic markers were cross-sectionally associated with a higher frequency of subclinical CVD, although the associations with individual markers varied depending on the vascular bed. These results suggest that the ultimate onset of CVD related to abnormal glucose metabolism likely represents the combined influence of different biological pathways leading to subclinical atherosclerosis in various vascular beds. Additional studies are warranted to confirm these findings longitudinally and evaluate the various biological pathways that determine glycemic-related atherosclerotic changes in various vascular beds. Overall, our findings are of contemporary significance given the rising burden of glucose intolerance in the United States, especially among blacks.

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Disclosures

None.

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