Diabetes Mellitus, Prediabetes, and Incidence of Subclinical Myocardial Damage

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Background—Persons with prediabetes and diabetes mellitus are at high risk for cardiovascular events. However, the relationships of prediabetes and diabetes mellitus to the development of subclinical myocardial damage are unclear.

Methods and Results—We measured cardiac troponin T with a highly sensitive assay (hs-cTnT) at 2 time points, 6 years apart, among 9051 participants of the community-based Atherosclerosis Risk in Communities Study with no diabetes mellitus, or prediabetes, and without cardiovascular disease including silent myocardial infarction by ECG. First, we examined the incidence of elevated hs-cTnT (≥14 ng/L) at 6 years of follow-up. Second, we examined clinical outcomes during the subsequent ≈14 years of follow-up among persons with and without incident elevations in hs-cTnT. Cumulative probabilities of elevated hs-cTnT at 6 years among persons with no diabetes mellitus, prediabetes, and diabetes mellitus were 3.7%, 6.4%, and 10.8%, respectively. Compared with normoglycemic persons, the adjusted relative risks for incident elevated hs-cTnT were 1.40 (95% CI, 1.08–1.80) for prediabetes and 2.47 (95% CI, 1.78–3.43) for diabetes mellitus. Persons with diabetes mellitus and incident elevations in hs-cTnT were at a substantially higher risk of heart failure (hazard ratio, 6.37 [95% CI, 4.27–9.51]), death (hazard ratio, 4.36 [95% CI, 3.14–6.07]), and coronary heart disease (hazard ratio, 3.84 [95% CI, 2.52–5.84]) compared with persons without diabetes mellitus and no incident elevation in hs-cTnT.

Conclusions—Prediabetes and diabetes mellitus were independently associated with the development of subclinical myocardial damage, as assessed by hs-cTnT, and those persons with evidence of subclinical damage were at highest risk for clinical events. These results support a possible deleterious effect of hyperglycemia on the myocardium, possibly reflecting a microvascular cause. **(*Circulation*. 2014;130:1374-1382.)**

Key Words: biological markers ■ diabetes mellitus ■ epidemiology ■ prediabetic state

Cardiovascular disease is the leading cause of death among persons with diabetes mellitus, and there is evidence that cardiac damage is often present at the time of clinical diagnosis of diabetes mellitus.[1,2] In addition, persons with hyperglycemia even below the threshold for the diagnosis of diabetes mellitus are known to be at high risk for cardiovascular events.[3–5] Elevated glucose levels are thought to induce hyperglycemia-mediated coronary microvascular dysfunction and result in myocardial injury.[6–11] Previous studies have shown that persons with prediabetes or diabetes mellitus have an increased prevalence of atherosclerosis, as measured by carotid intimal thickness or coronary artery calcium.[11–16] Much less is known about the relationships of prediabetes and diabetes mellitus with subclinical myocardial damage, particularly with respect to its progression over time.

Clinical Perspective on p 1382

Cardiac troponins are elevated in the setting of myocardial damage and are a standard measure used for the diagnosis of myocardial infarction. There have been several generations of increasingly sensitive tests that reliably detect lower and lower levels of troponin in the blood. A novel high-sensitivity assay for cardiac troponin T (hs-cTnT) developed by Roche Diagnostics allows for the reliable measurement of troponin far below the conventional limit of detection.[17] It has been suggested that cardiac troponin detected in asymptomatic persons with this novel assay may represent chronic subclinical myocardial injury, of a nonatherosclerotic origin,[18,19] with very strong associations with subsequent heart failure and death and only a moderate association with risk of coronary

Received February 13, 2014; accepted August 13, 2014.

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.114.010815/-/DC1.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.114.010815**

heart disease.[20] Previous studies have shown cross-sectional associations of diabetes mellitus with hs-cTnT.[21,22] However, the associations of diabetes mellitus and prediabetes with the progression of myocardial damage, as indicated by temporal changes in hs-cTnT concentrations in a community-based population, are unknown.

Our objective was to characterize the associations of diabetes mellitus and prediabetes with 6-year incidence of subclinical myocardial injury, as assessed by hs-cTnT, in a community-based population without clinically evident cardiovascular disease. We conducted secondary analyses to evaluate associations of the incident elevations in hs-cTnT with subsequent risk of coronary heart disease, heart failure, and all-cause mortality in persons with and without diabetes mellitus at baseline.

Methods

Study Population

The Atherosclerosis Risk in Communities (ARIC) study is a community-based, prospective cohort of 15 792 participants sampled from 4 US communities. The first clinic examinations (visit 1) took place from 1987 to 1989, with 3 follow-up visits approximately every 3 years.[23] A fifth visit was completed in 2011–2013. Institutional review boards at each clinical site reviewed the study, and informed consent was obtained from all of the participants. The second clinic examination (visit 2) took place from 1990 to 1992, was attended by 14 348 participants, and was the first ARIC visit with measurement of hs-cTnT. We excluded all persons who had coronary heart disease (including silent myocardial infarction detected by ECG), stroke, or heart failure at or before visit 2 (n=1542); were fasting <8 hours; were nonwhite or nonblack; were missing variables of interest (n=1763); were missing hs-cTnT measurement (n=41); had an hs-cTnT level ≥14 ng/L at visit 2 (n=376); or who were missing the follow-up hs-cTnT measurement at visit 4 in 1996–1998 (n=1575). Thus, there were 9051 participants included in our main study population (Figure I in the online-only Data Supplement). There were 604 incident cardiovascular events and 282 noncardiovascular deaths that occurred between visits 2 and 4 and were accounted for in our analyses. In secondary analyses of incident coronary heart disease, heart failure, and all-cause mortality risk among persons with and without incident elevations in hs-cTnT levels, we further excluded 160 persons who were missing covariates of interest at visit 4, for a study population of 8005 in our analyses of clinical events.

Definitions of Diabetes Mellitus and Prediabetes

Diabetes mellitus was defined as a self-reported physician diagnosis of diabetes mellitus, current use of glucose-lowering medications, or a hemoglobin (Hb) A1c value ≥6.5% at baseline. Among persons without diabetes mellitus, prediabetes was defined based on the clinical cut points for HbA1c of 5.7% to 6.4%.[24] In sensitivity analyses, we compared definitions of diabetes mellitus and prediabetes based on diagnostic cut points for HbA1c and fasting glucose.

Measurement of hs-cTnT

Cardiac troponin T was measured at 2 time points, 6 years apart, using the same highly sensitive (precommercial) sandwich immunoassay method (Roche Elecsys T, Roche Diagnostics, Indianapolis, IN). We measured hs-cTnT in stored serum samples collected at visit 2 (1990–1992) using a Roche Elecsys 2010 Analyzer (Roche Diagnostics) at the University of Minnesota in 2012–2013. We measured hs-cTnT in stored plasma samples collected at visit 4 (1996–1998) using a Cobas e411 analyzer (Roche Diagnostics) at Baylor College of Medicine. We conducted a formal calibration study (N=200 paired samples) to evaluate possible differences across specimen type and laboratory. No significant differences were observed, and statistical correction was not indicated.[25]

Other Variables

Serum glucose level was measured using the hexokinase method. HbA1c was measured in stored whole blood samples using high-performance liquid chromatography with instruments standardized to the Diabetes Control and Complications Trial assay (Tosoh A1c 2.2 and Tosoh G7).[26] Plasma lipid concentrations,[27–30] body mass index,[31] and blood pressure[32] were measured as part of the original ARIC study protocol. C-reactive protein was measured in 2012–2013 in stored serum samples (Roche Diagnostics). Hypertension was defined as the mean of the second and third readings at the visit (with cutoff for systolic blood pressure of ≥140 mm Hg and a cutoff for diastolic blood pressure of ≥90 mm Hg) or the use of hypertension medication. Participants reported their alcohol use and smoking status. Glomerular filtration rate was estimated from serum creatinine, age, sex, and race using the CKD-EPI 2009 equation.[33] Left ventricular hypertrophy was assessed using resting 12-lead electrocardiograms and defined by Cornell criteria.[34]

Incident Coronary Heart Disease, Heart Failure, and All-Cause Mortality

The ascertainment of deaths and classification and adjudication of cardiovascular events in ARIC have been published previously.[35,36] Briefly, any hospitalization was reported annually by participants or their proxy and also identified through surveillance of hospitals in each community. Trained personnel abstracted hospital records for potential cardiovascular events. Coronary heart disease events were adjudicated by an end points committee and were defined here as a definite or probable myocardial infarction, death from coronary heart disease, or cardiac procedure. Heart failure cases were identified from hospitalization diagnosis codes (*International Classification of Diseases*, *Ninth Revision*, code 428) and death surveillance (hospital discharge records for inpatient deaths and death certificates for deaths outside the hospital).[37]

Statistical Analyses

Elevated hs-cTnT was defined as a concentration of ≥14 ng/L, the previously reported 99th percentile for a healthy reference group of persons aged 20 to 70 years, as defined by the manufacturer of the assay.[20,38] We conducted prospective analyses to characterize the association of baseline diabetes mellitus and prediabetes status with progression of hs-cTnT from nonelevated (<14 ng/L) at baseline (1990–1992) to elevated (≥14 ng/L) at follow-up (1996–1998). We used multinomial logistic regression to estimate the relative risks of subclinical myocardial damage as defined by an incident elevation in hs-cTnT at the 6-year follow-up (visit 4) comparing persons with no diabetes mellitus, prediabetes, and diabetes mellitus at visit 2 and accounting for intervening cardiovascular events and deaths between visits 2 and 4. All of the multivariable models were adjusted for age (years), race-center (whites, Washington County; whites, Minneapolis; blacks, Jackson; blacks, Forsyth County; or whites, Forsyth County), sex (male or female), body mass index (in kilograms per meter squared), C-reactive protein (in milligrams per liter), smoking (current, former, or never), mean systolic blood pressure (in millimeters of mercury), low-density lipoprotein cholesterol (in milligrams per deciliter), high-density lipoprotein cholesterol (in milligrams per deciliter), triglycerides (in milligrams per deciliter), current use of hypertension medication (yes or no), current use of cholesterol-lowering medication (yes or no), estimated glomerular filtration rate (in milliliters per minute per 1.73 m^2), alcohol use (current, former, or never), and left ventricular hypertrophy (yes or no). We conducted sensitivity analyses excluding participants with hs-cTnT >30 ng/L at follow-up and stratified by race (black or white) or baseline category of hs-cTnT level (<5, 5–8, or 9–13 ng/L).

We conducted secondary analyses of the association of incident elevated hs-cTnT categories with subsequent risk of coronary heart

disease, heart failure, and all-cause mortality comparing risk in persons with no diabetes mellitus, prediabetes, and diabetes mellitus. We used Cox proportional hazards models with visit 4 as baseline and with follow up to January 1, 2012 (median follow-up of ≈14 years). Models were adjusted for all of the covariates as listed above but measured at visit 4. Model discrimination was assessed using the Harrell C-statistic,[39] and we assessed improvement in the C-statistic for the addition of elevated hs-cTnT to models containing all of the other covariates overall and, separately, in persons with diabetes mellitus. We also conducted sensitivity analyses to account for incident cases of diabetes mellitus between visits 2 and 4.

Results

In this study population of persons with no clinical cardiovascular disease and nonelevated hs-cTnT (<14 ng/L) at baseline, persons with prediabetes or diabetes mellitus were more likely to be older, black, and obese and more likely to have hypertension, high C-reactive protein, left ventricular hypertrophy, and a poorer lipid profile compared with persons without diabetes mellitus (Table 1). Diabetes status at baseline was also strongly associated with higher levels of hs-cTnT; the percentage of persons with a hs-cTnT level of 9 to 13 ng/L was 15.3% in those with diabetes mellitus compared with 6.2% among those without diabetes mellitus.

At the follow-up visit 6 years after baseline among persons who did not develop cardiovascular disease, 4.8% (n=395) of the study population had incident elevated hs-cTnT levels (≥14 ng/L); of these, 43.6% (n=172) had hs-cTnT levels of 9 to 13 ng/L at baseline, 36.7% (n=145) had hs-cTnT levels of 5 to 8 ng/L at baseline, and 19.7% (n=78) were undetectable

Table 1. Characteristics of Study Participants Without Clinical Cardiovascular Disease and hs-cTnT <14 ng/L at Baseline According to Prediabetes and Diabetes Mellitus Status (Visit 2, 1990–1992), From the Atherosclerosis Risk in Communities Study

Characteristic	Overall (n=9051)	No Diabetes Mellitus (HbA1c <5.7%; n=6259)	Prediabetes (HbA1c 5.7–6.4%; n=2090)	Diabetes Mellitus (Diagnosis or HbA1c ≥6.5%; n=702)
Age, mean (SD), y	56.6 (5.6)	56.2 (5.6)	57.5 (5.7)	57.6 (5.7)
Male sex	41.6	41.1	44.1	38.9
Black race	20.5	12.6	36.1	41.3
Current smoker	19.8	17.7	26.8	18.5
Current drinker	59.5	64.6	52.1	38.7
Hypertension	30.2	24.6	38.5	53.2
BMI categories, kg/m^2				
Normal weight (BMI <25)	32.5	38.6	22.5	10.9
Overweight (BMI 25–30)	40.7	41.5	40.7	34.5
Obese (BMI ≥30)	26.7	19.8	36.8	54.7
C-reactive protein, mg/L				
<1	25.4	30.4	16.6	9.6
1 to <3	38.5	39.5	38.9	29.1
≥3	36.1	30.1	44.5	61.3
LDL cholesterol, mg/dL				
<100 (optimal)	16.8	18.1	13.4	15.3
100–129 (near optimal)	32.2	33.8	30.2	25.3
130–159 (borderline high)	30.1	29.7	30.4	32.9
160–189 (high)	14.9	13.6	17.9	17.2
≥190 (very high)	6.0	4.8	8.1	9.3
High triglycerides (≥150 mg/dL)	27.6	24.4	30.7	44.2
Low HDL cholesterol (< 40 mg/dL)	26.3	23.3	30.9	37.8
Low eGFR creatinine (<60 mL/min per 1.73 m^2)	1.0	0.8	1.2	1.2
Left ventricular hypertrophy	1.7	1.2	2.8	3.5
Hs-cTnT categories, ng/L				
<5	69.2	72.9	64.1	52.6
5–8	23.1	20.9	26.3	32.1
9–13	7.8	6.2	9.6	15.3

Estimates are percentages unless otherwise indicated. BMI indicates body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; hs-cTnT, cardiac troponin T measured with a high-sensitivity assay; and LDL, low-density lipoprotein.

(hs-cTnT level <5 ng/L) at baseline 6 years prior (Table I in the online-only Data Supplement). Among those persons with incident hs-cTnT level ≥14 ng/L at the 6-year follow-up visit, the median (25th percentile, 75th percentile) hs-cTnT level was 17 ng/dL (15, 21 ng/dL).

Among those who remained free of cardiovascular disease over the follow-up period, persons with diabetes mellitus (7.4% of the population) and prediabetes (22.1% of the population) at visit 2 had a higher crude incidence of hs-cTnT ≥14 ng/L at visit 4 compared with persons without diabetes mellitus (Figure 1A). In multinomial regression models accounting for the competing risk of cardiovascular events or death between the 2 visits, diabetes mellitus and prediabetes were significantly associated with incident subclinical myocardial damage (incident hs-cTnT ≥14 ng/L) even after adjustment for cardiovascular risk factors (Figure 1B). The relative risks and 95% CIs comparing persons with prediabetes or diabetes mellitus defined by clinical categories of HbA1c with persons with no diabetes mellitus at visit 2 were 1.40 (95% CI, 1.08–1.80) and 2.47 (95% CI, 1.78–3.43), respectively (Figure 1B and Table II in the online-only Data Supplement).

Our results were not appreciably altered when persons with hs-cTnT values >30 ng/L (n=46) at the follow-up visit were excluded (data not shown). When diabetes mellitus and prediabetes were defined using fasting glucose criteria, a similar pattern but weaker associations with incident elevations in hs-cTnT were observed (Table II in the online-only Data Supplement). Interaction by race was not statistically significant (P for interaction=0.874), and race-stratified analyses showed similar patterns of association in black and white adults (Table III in the online-only Data Supplement). Analyses stratified by baseline category of hs-cTnT revealed that the strongest associations were observed among those persons with hs-cTnT levels ≤8 ng/L at baseline (Table 2).

In secondary analyses, we found that incident elevations in hs-cTnT were significantly associated with incident coronary heart disease, heart failure, and all-cause mortality (Figure 2 and Table IV in the online-only Data Supplement). For heart failure and mortality, there were robust and monotonic associations across groups defined by diabetes status within persons with and without incident elevated hs-cTnT. Those persons who developed subclinical myocardial damage as assessed by incident elevations in hs-cTnT had higher risks of heart failure and all-cause mortality even across diabetes categories compared with those persons who did not develop subclinical myocardial damage. Incident elevations in hs-cTnT were less strongly associated with coronary heart disease, and the overall pattern of association was somewhat less robust. Nonetheless, persons with incident elevated hs-cTnT and diabetes mellitus had substantially increased risks of heart failure (hazard ratio, 6.37 [95% CI, 4.27–9.51]), all-cause mortality (hazard ratio, 4.36 [95% CI, 3.14–6.07]), and coronary heart disease (hazard ratio, 3.84 [95% CI, 2.52–5.84]) compared with those with no incident elevations in hs-cTnT and without diabetes mellitus. These observed patterns with clinical events were similar in black and white adults (Table V in the online-only Data Supplement). In sensitivity analyses accounting for incident cases of diabetes mellitus that occurred in persons with no diabetes mellitus and prediabetes at visit 2, persons who developed diabetes mellitus during the follow-up period were at a higher risk of events compared with those who remained nondiabetic (Table VI in the online-only Data Supplement), and persons who remained in the prediabetes group over the 6-year period were at higher risk, particularly if hs-cTnT level was elevated.

When added to models with diabetes mellitus and all of the other covariates already included, elevations in hs-cTnT significantly improved model discrimination for heart failure (P<0.001) and death (P=0.005), but the improvement in the prediction for coronary heart disease was of only borderline significance (P=0.085; Table 3). Similar patterns were observed when the analyses were limited to persons with diabetes mellitus, although our power was correspondingly lower, with only 569 subjects in this group. The improvement in the C statistic for coronary heart disease was no longer statistically significant (P=0.173).

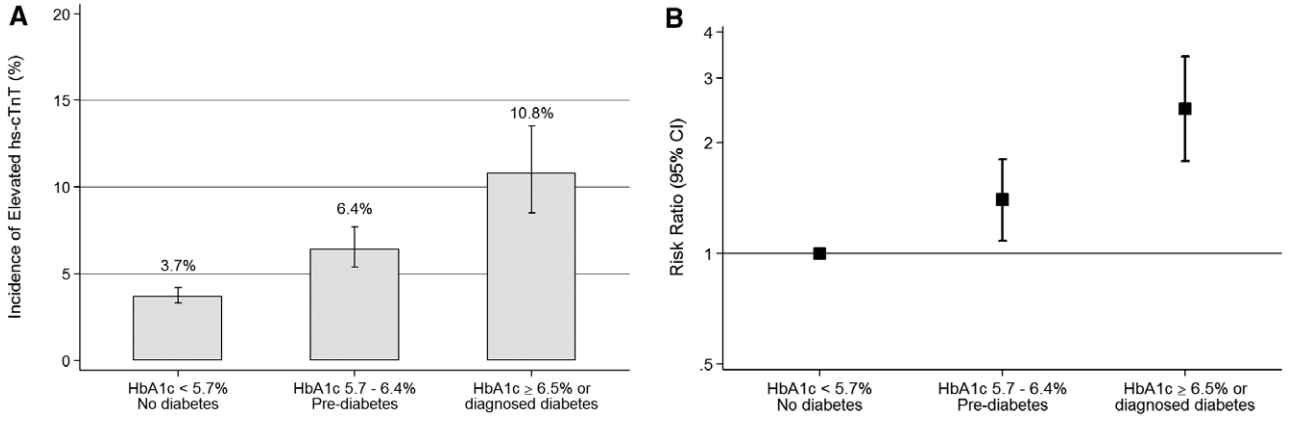

Figure 1. A, Cumulative incidence of elevated (≥14 ng/L) highly sensitive cardiac troponin T (hs-cTnT) at follow-up (visit 4, 1996–1998) according to categories of prediabetes and diabetes mellitus at baseline (visit 2, 1990–1992) among persons who remained free of cardiovascular disease during the follow-up period (n=8165). **B**, Adjusted risk ratios (95% confidence intervals [CIs]) for the association of prediabetes and diabetes mellitus with 6-year incident elevated (≥14 ng/L) according to prediabetes and diabetes mellitus at baseline (visit 2, 1990–1992; n=9051).

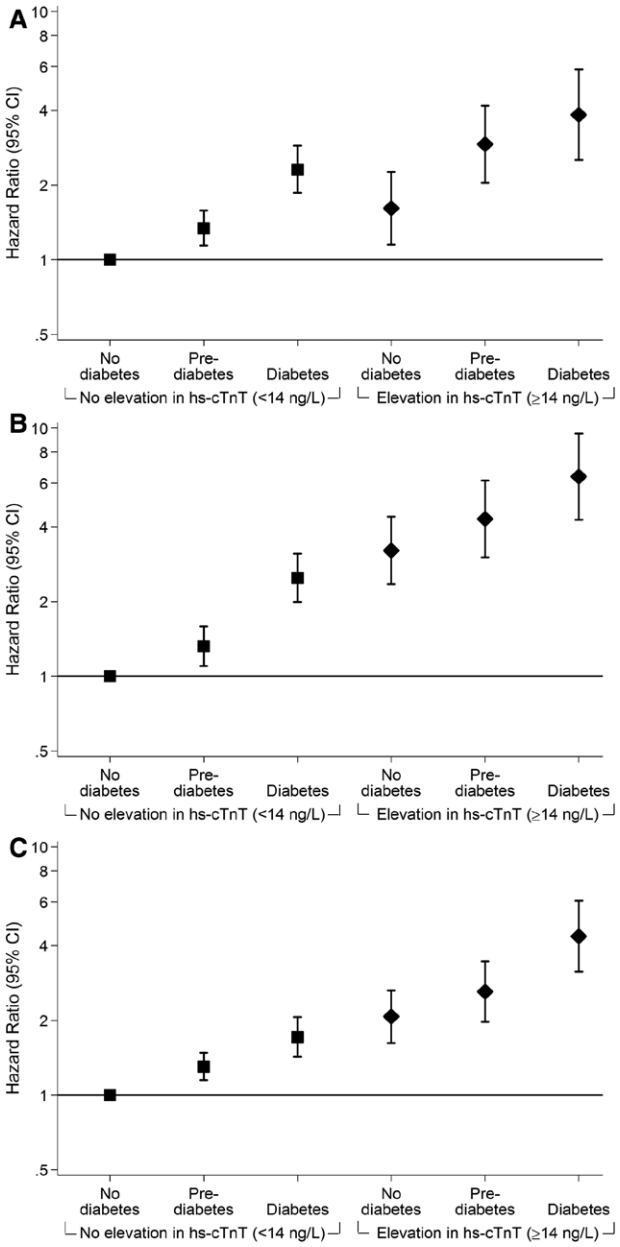

Figure 2. Adjusted hazard ratios (95% confidence intervals [CIs]) for the association of diabetes mellitus status with incident coronary heart disease (**A**), heart failure (**B**), and all-cause mortality (**C**) among persons with and without subsequent progression of myocardial damage as assessed by 6-year incident elevation (≥14 ng/L) in highly sensitive cardiac troponin T (hs-cTnT; n=8005).

Discussion

In this community-based population without clinical cardiovascular disease, we found that prediabetes and diabetes mellitus were significantly associated with the 6-year incidence of subclinical myocardial damage, as assessed by the elevation of cardiac troponin T detected with a novel highly sensitive assay. We further observed that these incident elevations in hs-cTnT were associated with future clinical outcomes, particularly heart failure and death.

In 2010, HbA1c was added to the tests recommended for use in the diagnosis of diabetes mellitus and the identification of persons at risk for diabetes mellitus.[40] Our results suggest that persons with prediabetes, when defined by HbA1c criteria, are at risk for not only the subsequent development of diabetes mellitus[3] but also for the progression of subclinical cardiac damage and ensuing cardiovascular events. There has been controversy regarding the categories used to define prediabetes, particularly the discordance between those persons identified using the recommended clinical cut points of 5.7% to 6.4% for HbA1c and 100 to 125 mg/dL for fasting glucose (impaired fasting glucose). Prediabetes, particularly when defined by HbA1c criteria, was associated with incident elevations of hs-cTnT and clinical outcomes, demonstrating that, whereas the prediabetes category of HbA1c identifies fewer people,[41] persons with HbA1c 5.7% to 6.4% are at a higher risk of progression of myocardial damage compared with persons with impaired fasting glucose.

The 99th percentile of hs-cTnT was 22 ng/L at end of the 6-year follow-up period in this study population of participants who remained free of cardiovascular disease. This is higher than 14 ng/L, the 99th percentile of the healthy reference population defined by the manufacturer. There is currently much debate regarding approaches to defining the reference ranges for highly sensitive cardiac troponin assays in the general population[42,43]; reference values for these assays in the population have not yet been established.

Given the controversy regarding the clinical implications of racial differences in HbA1c,[44,45] the lack of an interaction by race in our study is reassuring. We found that HbA1c diagnostic categories were associated with progression of myocardial damage and clinical outcomes in both blacks and whites, consistent with other studies suggesting no racial disparity in the prognostic value of HbA1c as a risk marker of microvascular or macrovascular outcomes.[46–48]

Persons with diabetes mellitus have a substantially elevated risk of cardiovascular events and death compared with persons without diabetes mellitus, even after accounting for major cardiovascular risk factors.[4,49] Previous studies have also established robust associations between cardiac troponin T measured by the same assay as studied here and the incident development of heart failure, stroke, coronary heart disease, and all-cause mortality in community-based populations.[20,50–52] A previous study has also shown that increases in hs-cTnT over 2 to 3 years are associated with a subsequent risk of heart failure and cardiovascular death.[50] We have shown previously a cross-sectional association between HbA1c and hs-cTnT in the ARIC cohort.[21]

Our results extend these previous findings and support a possible deleterious effect of hyperglycemic states on the myocardium. We also found that persons with prediabetes or diabetes mellitus who subsequently developed subclinical myocardial damage—as indicated by an incident elevation of hs-cTnT at the 6-year follow-up visit—were at highest risk of clinical events, particularly heart failure and mortality. Furthermore, those persons without diabetes mellitus but who had incident elevated hs-cTnT were at similar or higher risk of heart failure and mortality compared with persons with diabetes mellitus but no incident elevation in hs-cTnT. Indeed, hs-cTnT significantly improved risk stratification for heart failure

Table 2. Adjusted Risk Ratios (95% CIs) for the Association of Prediabetes and Diabetes Mellitus With 6-Year Incident Elevated (≥14 ng/L) hs-cTnT at Visit 4 (1996–1998) According to Diagnostic Categories of Prediabetes and Diabetes Mellitus Defined by HbA1c and Stratified by Baseline Category of hs-cTnT at Visit 2 (1990–1992)

	Baseline (Visit 2, 1990–1992) Troponin Group (n=9051)					
	<5 ng/L (n=6259)		5–8 ng/L (n=2090)		9–13 ng/L (n=702)	
HbA1c Diagnostic Criteria	n/N	RR (95% CI)	n/N	RR (95% CI)	n/N	RR (95% CI)
<5.7% (no diabetes)	42/4509	1 (reference)	78/1290	1 (reference)	94/383	1 (reference)
5.7–6.4% (prediabetes)	25/1344	2.03 (1.19–3.48)	40/552	1.19 (0.78–1.81)	51/201	0.98 (0.62–1.56)
Diabetes mellitus (≥6.5% or diagnosis)	11/406	3.34 (1.60–6.98)	27/248	2.30 (1.35–3.92)	27/118	1.40 (0.77–2.57)
P for trend*		<0.001		0.006		0.389

Data were adjusted for age (y), race-center (whites, Washington County; whites Minneapolis; blacks, Jackson; blacks, Forsyth County; and whites, Forsyth County), sex (male or female), body mass index (kg/m^2), C-reactive protein (mg/L), smoking (current, former, or never), mean systolic blood pressure (mm Hg), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), estimated glomerular filtration rate (mL/min per 1.73 m^2), current use of hypertension medication (yes or no), current lipid-lowering medication use (yes or no), alcohol use (current, former, or never), and left ventricular hypertrophy (yes or no). CI indicates confidence interval; HbA1c, hemoglobin A1c; hs-cTnT, cardiac troponin T measured with a high-sensitivity assay; and RR, risk ratio.

**P* values for linear trend were obtained by numbering the categories 1 through 3 and including this categoric variable as a linear term in the model.

and death in the overall population and among persons with diabetes mellitus.

It is noteworthy that hs-cTnT was strongly associated with microvascular risk factors (eg, hypertension and diabetes mellitus) and only weakly associated with traditional atherosclerotic risk factors (eg, low-density lipoprotein cholesterol). Our previous work is also consistent with this finding that hs-cTnT reflects cardiac damage occurring via nonatherosclerotic mechanisms.[21,53] The robust association between hyperglycemia and hs-cTnT may be mediated through microischemia because of the insufficiency of small intramyocardial arterioles (or possibly capillaries), reflecting primary small vessel disease, or it is possible that this may reflect myocardial hypertrophy, outstripping the capacity of the microvasculature to supply nutrients to the myocardium. Indeed, hyperglycemia-induced injury to the myocardium may be an important contributor to the growing epidemic of heart failure associated with diabetes mellitus and obesity.[54]

Recent large, randomized clinical trials of interventions to reduce cardiovascular risk in persons with diabetes mellitus or prediabetes have been disappointing.[55–59] Major advances in the medical management of lipids and blood pressure over the past several decades and evidence of possible adverse effects of glucose-lowering drugs have complicated the interpretation of contemporary trials designed to further lower cardiovascular risk in persons with diabetes mellitus. A concern is that these interventions have been too little, too late, focusing on reducing risk in high-risk persons often with a history of cardiovascular disease or a long duration of diabetes mellitus who are already being aggressively managed. Recent trials have focused of the relatively narrow end point of combined hard cardiovascular events, typically incorporating fatal and nonfatal myocardial infarction, stroke, and coronary

Table 3. C Statistics and Differences in C Statistics for Clinical Events (Coronary Heart Disease, Heart Failure, and All-Cause Mortality) From Models With and Without Incident Elevated hs-cTnT in the Overall Population and Among Persons With Diabetes Mellitus

	Coronary Heart Disease			Heart Failure			All-Cause Mortality		
Model	C Statistic	Difference	*P* Value	C Statistic	Difference	*P* Value	C Statistic	Difference	*P* Value
Overall population (n=8005)									
Base model*	0.7093	Reference	-	0.7447	Reference	-	0.7199	Reference	-
+ elevated hs-cTnT	0.7118	0.0025	0.085	0.7541	0.0094	<0.001	0.7237	0.0038	0.005
Persons with diabetes mellitus (n=569)									
Base model*	0.6519	Reference	-	0.6860	Reference	-	0.6871	Reference	-
+ elevated hs-cTnT	0.6551	0.0033	0.173	0.6998	0.0139	0.001	0.6941	0.0070	0.002

hs-cTnT indicates cardiac troponin T measured with a high-sensitivity assay; HbA1c, hemoglobin A1c.

*Base model includes: age (y), race-center (whites, Washington County; whites, Minneapolis; blacks, Jackson; blacks, Forsyth County; and whites, Forsyth County), sex (male or female), diabetes mellitus status (HbA1c <5.7%, HbA1c 5.7% to 6.4%, diabetes mellitus diagnosis or HbA1c ≥6.5%), body mass index (kg/m^2), C-reactive protein (mg/L), smoking (current, former, or never), mean systolic blood pressure (mm Hg), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), estimated glomerular filtration rate (mL/min per 1.73 m^2), current use of hypertension medication (yes or no), current lipid-lowering medication use (yes or no), alcohol use (current, former, or never), and left ventricular hypertrophy (yes or no). In the analysis limited to persons with diabetes mellitus, diabetes status was not included in the model.

heart disease. The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus trial did demonstrate a significant reduction in cardiovascular risk (an a priori secondary outcome) in a high-risk prediabetes population treated with acarbose compared with placebo, although the total number of cardiovascular events was small (n=15 in the treatment arm and n=32 in the placebo arm).[60] Nevertheless, there are scant data on the effect of glucose-lowering interventions in persons with prediabetes or diabetes mellitus with no clinical cardiovascular disease at the outset.

The current study had several limitations. We only had 2 measurements of hs-cTnT, 6 years apart, to characterize the progression of myocardial damage. Adjustment for left ventricular hypertrophy was limited to assessment using ECG data only, and, despite rigorous adjustment for potential confounding factors including demographics, blood pressure, lipids, adiposity, kidney function, and medication use, we cannot eliminate the possibility of residual confounding in this observational setting. Strengths of this study include the large community-based sample, rigorous measurement of traditional cardiovascular risk factors, and the availability of HbA1c and fasting glucose measurements to characterize prediabetes. The long-term follow-up of the ARIC cohort and active surveillance for cardiovascular events and deaths allowed us to conduct secondary analyses of incident cardiovascular outcomes.

In summary, this study provides evidence for a deleterious effect of hyperglycemia on the myocardium, even below the threshold for a diagnosis of diabetes mellitus. Furthermore, those persons with evidence of incident subclinical myocardial damage were at high risk for future mortality and cardiovascular events, particularly heart failure. With the growing dual epidemics of obesity and diabetes mellitus, these results underscore the importance preventing progression to early hyperglycemic states and the development of diabetes mellitus. Our results suggest that primary and secondary prevention of atherosclerotic disease in diabetes mellitus, for example, via statin therapy, may not be sufficient to fully address the cardiac risk associated with hyperglycemic states.

Acknowledgments

We thank the staff and participants of the ARIC Study for their important contributions. Reagents for the high-sensitivity cardiac troponin and C-reactive protein assays were donated by Roche Diagnostics.

Sources of Funding

This research was supported by National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases grant R01 DK089174 to Dr Selvin. The ARIC study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN 268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN26820 1100012C).

Disclosures

Drs Hoogeveen and Ballantyne have received grant support from Roche Diagnostics and are coinvestigators on a provisional patent filed by Roche for use of biomarkers in heart failure prediction. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Persons with prediabetes and diabetes mellitus are at high risk for cardiovascular events. However, the relationships of prediabetes and diabetes mellitus to the development of subclinical myocardial damage are unclear. We evaluated the associations of diabetes mellitus and prediabetes with the development of subclinical myocardial damage, as assessed by an incident elevation (≥14 ng/L) in cardiac troponin T measured with a highly sensitive assay during 6 years of follow-up. We also evaluated the subsequent risk of cardiovascular events and deaths by diabetes mellitus status among those persons with and without incident elevations in the high-sensitivity assay for cardiac troponin T. We found that both prediabetes and diabetes mellitus were independently associated with the development of subclinical myocardial damage. Furthermore, those persons with evidence of incident subclinical myocardial damage were at high risk for the future mortality and cardiovascular events, particularly heart failure. These results support a possible deleterious effect of hyperglycemia on the myocardium, possibly reflecting a microvascular cause. With the growing dual epidemics of obesity and diabetes mellitus, these results underscore the importance of preventing progression to early hyperglycemic states and the development of diabetes mellitus. Our results suggest that primary and secondary prevention of atherosclerotic disease in diabetes mellitus, for example via statin therapy, may not be sufficient to fully address the cardiac risk associated with hyperglycemic states. There is a possibility that the major improvements we have seen in cardiovascular morbidity and mortality over the past several decades may be disrupted by the epidemic of diabetes mellitus and prediabetes.