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Relation of glycemic status with unrecognized MI and the subsequent risk of mortality: The Jackson Heart Study

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ABSTRACT

Background: Almost 1/3 to 1/2 of initial myocardial infarctions (MI) may be silent or unrecognized (UMI), which forecasts future clinical events. Further, limited data exist to describe the potential risk for UMI in African-Americans. The relationship of glucose status with UMI was examined in the Jackson Heart Study: a cohort of African-American individuals.

Methods and results: At baseline, there were 5,073 participants with an initial 12-lead electrocardiogram (ECG) and fasting glucose measured. Of these participants, 106(2.1%) had a UMI, and 268(4.2%) had a recognized MI. This population consisted of 3,233 (63.7%) participants with normal fasting glucose (NFG), 533 (10.5%) with IFG, and 1,039 (20.4%) with DM. Logistic regression investigated the relationship between glucose status and UMI. Cox proportional hazard models determined the significance of all-cause mortality during follow-up by MI status. The sample was 65% female with a mean age of 55.3 ± 12.9 years. Over a mean follow-up of 10.4 years, there were 795 deaths. Relative to NFG, the crude odds ratio (OR) estimates for UMI at baseline with IFG and DM were 1.00(95% CI:0.48–2.14) and 3.22(2.15–4.81), respectively. With adjustment, DM continued to be significantly associated with UMI [2.30 (1.42–3.71)]. Overall, participants with a baseline UMI had an adjusted Hazard ratio (HR) of 2.00(1.39–2.78) of death compared to no prior MI. Compared to those with no MI, those with a recognizedMI had an adjusted HR of 1.70(1.31–2.17) for mortality.

Conclusions: DM is associated with UMI in African-Americans. Further, a UMI carried similar risk of death compared to those with a recognized MI.

Silent and unrecognized myocardial infarctions (UMI) comprise a significant proportion of atherosclerotic coronary events. Differing cohorts have found 1/3rd to 1/2 of all myocardial infarctions may be silent [1,2]. Data suggest that UMIs may carry the same prognosis as clinically-recognized coronary events [3–9], and in some cases, may carry a worse prognosis [10,11]. Historically, diabetes mellitus, age, and hypertension have significant associations with UMI. While neuropathy accounts for the mechanism of risk for UMI afforded by diabetes mellitus, limited data suggest that neuropathy may initiate while patients are pre-diabetic. Further, emerging data suggest that pre-diabetes may pre-dispose individuals to UMI.

Historically, African-Americans carry a disproportionate burden from diabetes mellitus and pre-diabetes. Using NHANES data, over 20% of African-Americans were diagnosed with diabetes mellitus and over one-third having pre-diabetes [12,13]. Given the paramount role of abnormal glucose metabolism in experiencing UMIs, African-Americans theoretically may be at a higher risk of developing a UMI. However, previous studies present conflicting data. Using MRI in the Multi-Ethnic Study of Atherosclerosis, 9% of African-Americans experienced a UMI, which was higher than Hispanics and Chinese ethnicities, but similar to Caucasians [14]. Earlier analyses from the Atherosclerosis Risk in Communities studies suggested that African-Americans had a slightly higher risk of UMI relative to Caucasians [1]. To clarify the burden and significance of UMI in African-Americans, we turned to the Jackson Heart Study to describe these relationships.

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1. Methods

The Jackson Heart Study is a prospective community-based observational study initiated in 2000 to investigate risk factors for cardiovascular disease in African Americans [15]. All participants provided written informed consent, and study protocols were approved by local institutional review boards. The study recruited participants from the Jackson, Mississippi, cohort of the Atherosclerosis Risk in Communities (ARIC) study and from the overall tri-county population, as described previously [16]. Participants completed 3 study visits: exam 1 between September 2000 and March 2004, exam 2 between October 2005 and December 2008, and exam 3 between February 2009 and January 2013. Data collected include demographic characteristics, morbid conditions, medications, laboratory test results, and cardiac test results, including electrocardiogram (exams 1 and 3 only) and echocardiogram (exam 1 only) [17]. The details of visit procedures, including supine 12-lead digital electrocardiography, have been described previously [17]. The definitions of comorbid conditions and the details of electrocardiography measurements and medication collection and coding [18,19] have also been reported. The Jackson Heart Study cohort surveillance system collects follow-up data on all participants, including deaths, study terminations (from 2000 through 2014), and heart failure hospitalizations (from 2005 through 2014) [20]. To ascertain all-cause mortality, participants was ascertained through annual follow-up interviews, death records from the Mississippi State Health Department, obituaries and the National Death Index.

2. Fasting glucose status

Individuals in the study were initially classified into one of three groups based on the fasting glucose criteria established by the American Diabetes Association [21]. These groups included normal fasting glucose (NFG; fasting glucose level < 100 mg/dL), impaired fasting glucose (IFG; fasting glucose level 100–125 mg/dL), and diabetes mellitus (DM; fasting glucose level > 125 mg/dL, previous diagnosis of diabetes, or taking insulin or oral hypoglycemic agents). For the purposes of this study, impaired fasting glucose is referred to as prediabetes.

3. 12-lead Electrocardiograms

Standard 12 lead ECGs were digitally acquired using a Marquette MAC–PC electrocardiograph (Marquette electronics, Milwaukee, Wisconsin) at 10 mm/mV calibration and speed of 25 mm/*sec*. All ECGs were read centrally and visually inspected for technical errors or inadequate quality. Standard 12 lead ECGs were obtained during the baseline exam. To diagnose a UMI, only the ECG from exam 1 was used.

The definition used for UMI was consistent with previous publications. [2] Using Minnesota ECG code, an unrecognized myocardial infarction was defined as the presence of major Q waves that met the specific standards or the combined presence of smaller Q waves and significant ST–T–wave abnormalities in a participant without a clinical history of a myocardial infarction [22].

Any participant with a self-reported history of a myocardial infarction at the baseline exam was counted as having had a recognized myocardial infarction.

4. Covariates

During baseline exam, medical histories and physical exams were performed to obtain clinical information. Fasting blood samples and physical measurements were obtained at the baseline examination [23]. Resting, seated systolic and diastolic blood pressure (BP) were measured using the auscultatory method while having the mid-height of the cuff at heart level [24]. The seated (right arm) BP reading was an average of two systolic and diastolic measurements with at least 30 s between measurements. Hypertension was defined as the use of an antihypertensive medication or BP$\geq$ 140/90 mmHg. Smoking status was divided into 3 groups: never, former, and current, which was defined as having smoked within the past 30 days. Left ventricular hypertrophy was identified based on the baseline ECG.

5. Statistical analyses

Baseline characteristics were described for NFG, IFG, and DM. ANOVA and chi-square tests were performed to test for differences in baseline characteristics between the groups, with NFG serving as our reference. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS software version 9.1 (SAS Institute, Inc.; Cary, NC).

The unadjusted relationship between fasting glucose status and baseline UMI was initially described by logistic regression. Crude odds ratios were generated followed by adjustment for baseline demographics, including age, sex, and body mass index (Model 1), and additional adjustment for other covariates, including hypertension, systolic BP, smoking, total cholesterol, and HDL cholesterol (Model 2). Next, stepwise regression was performed to identify those risk factors most closely associated with UMI. To determine the potential association between different MI types (none, baseline recognized, and baseline unrecognized) and all-cause mortality, Kaplan-Meier curves were generated. To further describe these relationships, crude and adjusted Cox proportional hazard ratios were generated. Adjustment was initially made for age, sex, and body mass index (Model 1) with additional subsequent adjustment for other baseline covariates, including fasting glucose status, aspirin use, statin use, hypertension, systolic BP, smoking, total cholesterol, and HDL cholesterol (Model 2).

6. Results

After excluding those with missing data, the study population consisted of 4805 participants. Their characteristics by fasting glucose status are shown in Table 1. The overall cohort was 100% African-American with a mean age of 55 $\pm$ 12 years. Participants with normal fasting glucose had a significantly lower mean BMI than those with IFG or DM (30.8, 32.7, and 34.2 kg/m^2, respectively). In addition, they also had significantly lower prevalence of hypertension (46%, 71%, 81%). At baseline, there were 106 patients with a UMI [49 NFG (1.5%), 8 IFG (1.5%), and 49 DM (4.72%); $p<0.001$] and 268 with a recognized MI, which means that 28.3% of all MIs were unrecognzed or silent. During

Table 1
Baseline characteristics.

	Normal Fasting Glucose (n = 3233)	Impaired Fasting Glucose (n = 533)	Diabetes Mellitus (n = 1039)
Age (years)	52.9 $\pm$ 13.1	59.3 $\pm$ 11*	60.7 $\pm$ 10.6*
Women (%)	2094 (64%)	305 (60%)	697 (66%)
Body Mass Index (kg/m^2)	30.8 $\pm$ 7.1	32.7 $\pm$ 7.0*	34.2 $\pm$ 7.1*
Height (cm)	168 $\pm$ 9.3	169 $\pm$ 90	168 $\pm$ 9.1
Weight (kg)	87 $\pm$ 21	93 $\pm$ 19	97 $\pm$ 21
Total Cholesterol (mg/dL)	198 $\pm$ 39	203 $\pm$ 39	200 $\pm$ 44
HDL Cholesterol (mg/dL)	52.8 $\pm$ 14.8	50.0 $\pm$ 14.2*	49.0 $\pm$ 13.7*
Hypertension, n (%)	1434 (46%)	371 (71%)*	837 (81%)*
Glomerular Filtration Rate (mL/min/1.73 m^2)	87.2 $\pm$ 17.0	83.8 $\pm$ 17.0*	83.0 $\pm$ 22.7*
Current smoker (%)	414 (13%)	69 (13%)	107 (11%)
Left Ventricular Hypertrophy (%)	270 (9%)	60 (11%)	145 (15%)*

Baseline characteristics divided fasting glucose status and diagnosis of diabetes mellitus. The (*) indicates a p-value <0.05 in comparison with the normal fasting glucose group.

follow-up, 795 participants (15%) died.

To determine if fasting glucose was associated with UMI at baseline, logistic regression models were generated (see Table 2). Without adjustment, DM had an odds ratio (OR) of 3.22 [95% confidence interval (CI: 2.15–4.81; $p < 0.001$] for UMI relative to NFG, but IFG had an OR of 1.00 (95% CI: 0.48–2.14) relative to NFG. With adjustment for age, sex, and body mass index, DM continued to be associated with UMI with an OR of 2.34 (95% CI: 1.53–3.57; $p < 0.001$). After further adjustment for hypertension, systolic BP, smoking status, total cholesterol, and HDL cholesterol, DM remained significantly associated with UMI [OR: 2.30 (95% CI: 1.42–3.71; $p < 0.001$). To further clarify the relationships between risk factors and demographics with UMIs, we performed a stepwise logistic regression model to identify the most significant associations (see Table 3 for the final model results).

To determine if UMIs carried the same level of risk for death as a recognized MI, we initially generated Kaplan-Meier curves to compare outcomes between those with a recognized MI, a UMI, and no MI. Both a recognized MI and a UMI carried increased risk of death during follow-up relative to those with no MI history ($p < 0.001$; see Fig. 1). These results were then stratified by fasting glucose status (see Fig. 2). For both NFG and DM, they elicited the same pattern with statistical significance. In IFG, the overall pattern also was seen but did not achieve statistical significance. Next, Cox proportional hazard models were generated to compare the different types of MI. Crudely, both a recognized MI and a UMI at baseline were associated with all-cause mortality ($p<0.001$ and $p<0.001$, respectively; see Table 4). With adjustment, these associations continued to be significant ($p<0.001$ and $p<0.001$, respectively). In stratified analyses, these associations were also observed in those with NFG and DM. The pattern was also seen in IFG but failed to reach statistical significance due to limited numbers

7. Discussion

There are several important observations that can be made based upon these analyses. First, the presence of an unrecognized myocardial infarction in African-Americans heralds an increased risk of mortality similar to having a recognized history of a myocardial infarction.. Second, diabetes mellitus is a significant risk factor for a UMI in African-Americans. Third, in spite of an increased prevalence of hypertension in African-Americans, the prevalence of UMI (2.2%) was consistent with other studies in populations with less hypertension, such as the Multi-Ethnic Study of Atherosclerosis (2%) and the Cardiovascular Health Study (3.4%). [2,25]

While health care outcomes have improved for African-Americans [26–29], there continue to be areas of disproportionate burden that need remedy [30–33]. Based on the analyses presented, a UMI carried similar survival to those with a recognized history of a myocardial infarction. As such, those individuals with a UMI may be under-treated in regards to their subsequent risk for cardiovascular disease and mortality. Screening for UMIs in an otherwise asymptomatic population presents pressing challenges, particularly as it relates to economics. Further studies are needed to help direct clinicians in whom and how to screen for UMIs. Given the strong association between DM and UMIs, perhaps initial efforts could focus on abnormal glucose metabolism. While DM remains a critical risk factor leading to UMI, IFG remains a suspect in need of evidence. Future efforts may need to focus on 2-hour oral glucose tolerance test as a measure to assess abnormal glucose metabolism.

The mechanism in how DM predisposes individuals to UMIs most likely relates to the development of autonomic neuropathy [34–36], By impairing nerve function, the pain signals which indicate an acute myocardial injury never reach the central nervous system. While DM stands as a significant risk factor for neuropathy, emerging evidence suggests that neuropathy may start early during the development of IFG, which would serve as further justification for investigating IFG's relationship to UMI [37–41], Unfortunately, once neuropathy develops, it

Table 2
Crude and adjusted odds ratios for unrecognized and recognized myocardial infarction by different fasting glucose groups.

	Crude Odds Ratio for Unrecognized MI	Crude Odds Ratio for Recognized MI	Odds Ratio for Unrecognized Myocardial Infarction: Model 1	Odds Ratio for Recognized MI: Model 1	Odds Ratio for Unrecognized Myocardial Infarction: Model 2	Odds Ratio for Recognized MI: Model 2						
IFG vs NFG	1.00 (0.48–2.14)	NS	2.11 (1.46–3.06)	<0.001	1.05 (0.43–2.60)	NS	1.55 (1.06–2.28)	0.023	1.07 (0.32–2.79)	NS	1.35 (0.92–2.00)	NS
DM vs NFG	3.22 (2.15–4.81)	< 0.001	3.16 (2.41–4.14)	<0.001	2.34 (1.53–3.57)	< 0.001	2.27 (1.71–3.03)	<0.001	2.30 (1.42–3.71)	< 0.001	1.54 (1.11–2.14)	<0.01

Model 1 adjusts for age, sex, and body mass index; Model 2 adjusts for Model 1 + hypertension, systolic blood pressure, tobacco use, total cholesterol, HDL cholesterol.

Table 3
Significant risk factors for UMI identified by stepwise regression model.

Stepwise Regression Significant Risk Factor	*P*-Value
Age	0.002
Male sex	0.058
Systolic Blood Pressure	<0.001
Diastolic Blood Pressure	0.024
Fasting Blood Glucose	0.043
Total Cholesterol	0.025
EKG Left Ventricular Hypertrophy	0.002

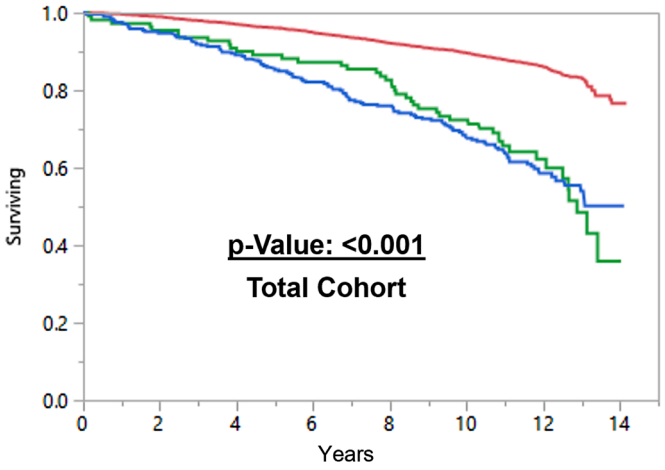

Fig. 1. Kaplan-Meier curves of all-cause mortality by MI-type: red: no myocardial infarction; green: unrecognized myocardial infarction; blue: recognized myocardial infarction.

rarely resolves. Hence, consideration and further study should be given to whether selective screening in those with neuropathy may represent an appropriate strategy for identifying and treating UMIs.

Previous studies have alluded to the strong association between hypertension and UMIs [42–46]. Even in these analyses, hypertension remained a critically significant risk factor. Most likely the relationship between hypertension and UMIs is simply mediated by the role of hypertension in atherosclerosis progression. There are no strong links between hypertension and neuropathy apart from abnormal glucose metabolism which could justify that mechanism accounting for the association. Further, if there was a particular mechanism between hypertension and UMIs, the prevalence of UMIs in this cohort would be much more prevalent than other cohorts, but instead, the prevalence is similar.

As with all studies, the analyses presented in this manuscript have limitations which must be considered. First, the 12-lead electrocardiogram has limited sensitivity and specificity for detecting myocardial infarctions [14]. In other studies, cardiac MRI with late gadolinium enhancement has proven to be a robust method, but the cost associated with it, as well as its limited availability, prohibits its wide-scale usage. Second, it remains difficult as to which test best identifies African-Americans with abnormal glucose metabolism without overt DM. Future studies may be best served by performing a 2-hour oral glucose tolerance test to assess the functionality of the participant's glucose metabolism. Third, with this cohort having a high prevalence of hypertension, the presence of left ventricular hypertrophy on the 12-lead electrocardiogram may obscure the expected findings of a myocardial infarction and lead to an under-reporting of those who may have experienced a UMI. [47] Fourth, the history of a previously recognized myocardial infarction was based solely on the participant's self-report during the baseline exam, which introduced potential recall bias. Finally, because glycemic status and UMI were assessed at the same point in time, it cannot be determined which condition occurred first.

8. Conclusion

Diabetes mellitus is strongly associated with UMI. Further, in this African-American cohort, UMI by ECG carried the same prognosis as those with a clinically-recognized myocardial infarction. Future studies

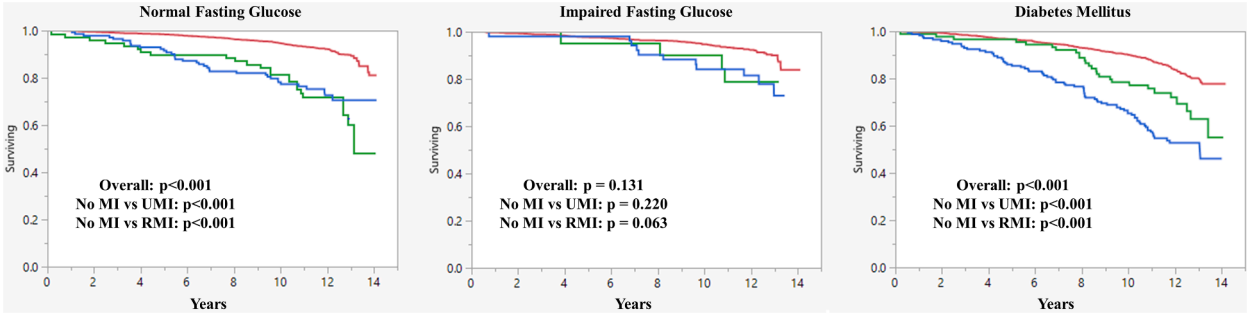

Fig. 2. Kaplan-Meier curves of all-cause mortality by MI-type stratified by glycemic status: red: no myocardial infarction; green: unrecognized myocardial infarction; blue: recognized myocardial infarction.

Table 4
Crude and adjusted hazard ratios for all-cause mortality comparing known (prior MI) and UMI to no MI.

Overall Cohort	Hazard Ratio Crude	Hazard Ratio Model 1	Hazard Ratio Model 2			
UMI vs No MI	3.32 (2.42–4.44)	< 0.001	2.24 (1.63–3.00)	< 0.001	2.00 (1.39–2.78)	<0.001
Prior MI vs No MI	3.43 (2.80–4.18)	< 0.001	2.10 (1.71–2.56)	< 0.001	1.70 (1.31–2.17)	< 0.001
NFG Cohort						
UMI vs No MI	4.69 (2.85–7.25)	< 0.001	2.80 (1.70–2.96)	< 0.001	2.65 (1.57–4.20)	<0.001
Prior MI vs No MI	3.61 (2.50–5.05)	< 0.001	2.10 (1.44–2.96)	< 0.001	2.02 (1.33–2.94)	0.001
IFG Cohort						
UMI vs No MI	1.92 (0.31–6.10)	0.410	1.74 (0.28–5.63)	0.482	1.39 (0.21–5.00)	0.676
Prior MI vs No MI	1.83 (0.89–3.38)	0.097	1.31 (0.63–2.42)	0.444	1.40 (0.66–2.67)	0.361
DM Cohort						
UMI vs No MI	2.09 (1.33–3.12)	< 0.001	1.68 (1.07–2.51)	0.024	1.57 (0.89–2.59)	0.117
Prior MI vs No MI	2.67 (1.99–3.54)	< 0.001	2.01 (1.49–2.67)	< 0.001	1.75 (1.16–2.55)	0.009

will be needed to better define the risk of a UMI in those with pre-diabetes.

Disclaimer

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