ARIC Manuscript Proposal #2430

PC Reviewed: 9/9/14 Status: A Priority: 2
SC Reviewed: _________ Status: _____ Priority: _____

1.a. Full Title: Racial differences in hyperglycemia: A comparison of traditional and nontraditional glycemic markers with diabetes, kidney disease, cardiovascular events and mortality

b. Abbreviated Title (Length 26 characters): Hyperglycemia and race

2. Writing Group:
   Writing group members: Christina M. Parrinello, Nisa M. Maruthur, A. Richey Sharrett, Ronald Klein, Richard Bergenstal, Morgan E. Grams, Josef Coresh, Elizabeth Selvin; others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __CMP__ [please confirm with your initials electronically or in writing]

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. **Timeline:** Upon approval of this manuscript proposal, we plan to submit a draft of the completed manuscript for internal review within a year.

4. **Rationale:**

The higher HbA1c values observed in blacks and other racial/ethnic minorities compared to whites are well-documented and controversial.\(^1^\text{--}^6\) Even among persons with similar levels of fasting glucose, blacks tend to have higher HbA1c compared to whites.\(^4^,^7\) This discrepancy has led to controversy over the use of HbA1c as a diagnostic test in blacks and other racial/ethnic minority groups. Proponents of race-specific cut-points for HbA1c have argued that HbA1c is artificially high in blacks due to non-glycemic factors (typically, hemoglobin glycation and red cell turnover have been suggested), and that the use of HbA1c may lead to overdiagnosis of diabetes in blacks.\(^8\) However, there is currently no direct evidence of racial differences in non-glycemic factors. It is likely that black and white persons may have differences in dietary patterns, physical activity, glucose metabolism, or other more proximal factors such as socioeconomic status, resulting in higher average circulating non-fasting glucose in blacks compared to whites, but this is unproven.\(^9\) If blacks have higher HbA1c via glycemic pathways, then blacks may actually have a higher absolute risk of diabetes and glycemia-related outcomes than whites.

Fructosamine, glycated albumin and 1,5-anhydroglucitol (1,5-AG) are extracellular serum measures of hyperglycemia, which are not affected by hemoglobin characteristics and red cell turnover. We have previously shown that HbA1c, fructosamine, and glycated albumin were higher and 1,5-AG was lower in black persons compared to white persons in a subset (n≈1700) of ARIC participants, even after adjustment for potential confounders and fasting glucose.\(^1\) The similar racial differences for serum markers of hyperglycemia provide evidence that non-glycemic factors such as hemoglobin glycation or red cell turnover do not explain the observed racial disparity.\(^1\)

Recent studies have shown similar relative associations of HbA1c with prevalent retinopathy\(^10\) and incident chronic kidney disease (CKD) and cardiovascular disease (CVD)\(^11\) in blacks and whites. This suggests that the utility of HbA1c for screening and diagnosis may be similar across ethnic groups and that the higher HbA1c in blacks is reflective of a true heightened state of hyperglycemia. Prospective associations of serum measures of hyperglycemia with micro- and macrovascular complications according to race have not been characterized and could shed further light on this controversy. We propose to rigorously characterize the association of nontraditional markers of hyperglycemia with clinical outcomes in blacks and whites and compare these associations to those observed for fasting glucose and HbA1c.
5. Main Hypothesis/Study Questions:

**Aim 1:** To compare baseline levels of glycemic markers by race in persons with and without diabetes, before and after adjustment for demographic and clinical variables.  
**Hypothesis 1:** Blacks have higher levels of hyperglycemia compared to whites, as indicated by all measures (higher fasting glucose, HbA1c, fructosamine and glycated albumin; and lower 1,5-AG).

**Aim 2:** To compare the associations of traditional and nontraditional markers of hyperglycemia with clinical outcomes (retinopathy, diabetes, CKD/end-stage renal disease [ESRD], CHD, stroke, heart failure and mortality) in black and white adults with and without diabetes.  
**Hypothesis 2:** Relative associations of HbA1c and serum glycemic markers with clinical outcomes will be similar by race although blacks will be at higher absolute risk of complications compared to whites. (We expect that relative associations of fasting glucose with outcomes will be weaker in blacks compared to whites, but that interactions will not be statistically significant.)

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

**Study design**

We will include all ARIC participants who attended visit 2 and have data available for all traditional and nontraditional glycemic markers, as well as for all covariates. We will exclude non-black and non-white participants. We will further exclude persons with prevalent disease from prospective analyses (e.g. persons with prevalent CVD at visit 2 from analyses of cardiovascular events).

**Exposures**

We will conduct analyses using traditional and nontraditional glycemic markers: fasting glucose, HbA1c, fructosamine, glycated albumin and 1,5-AG. All biomarkers were measured using specimens collected during ARIC visit 2. Fasting glucose was measured from serum at the University of Minnesota (UMN) with the Coulter DACOS Analyzer (Coulter Instruments) using a hexokinase method. HbA1c was measured from whole blood with the Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer and Tosoh G7 Analyzer (Tosoh Bioscience, Inc., South San Francisco, CA) using a high-performance liquid chromatography method. Fructosamine, glycated albumin and 1,5-AG were measured from serum in 2012-13 at UMN with the Roche Modular P800 (Roche Diagnostics Corporation, Indianapolis, IN). Fructosamine (Roche Diagnostics Corporation, Indianapolis, IN) was measured using a colorimetric method. Glycated albumin (Asahi Kasei Lucica GA-L, Tokyo, Japan) and 1,5-AG (GlycoMark) were measured using an enzymatic method.
Covariates

Self-report of diabetes diagnosis and use of glucose-lowering medications was asked at each clinic visit and annually since visit 4 during a telephone follow-up survey. Prevalent diabetes will be defined as diagnosis of diabetes or medication use at the current or any previous visit. Prevalent CVD will be defined using self-reported history of CHD, stroke or heart failure at visits 1 or 2, or hospitalization for any of these events prior to visit 2. Prevalent CKD will be defined using creatinine-based estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² at visit 2.

We will include the following covariates as potential confounders: age, gender, duration of diabetes, education level, alcohol consumption, smoking status, physical activity (Baecke sport activity index), systolic blood pressure, diastolic blood pressure, antihypertensive medication use, cholesterol-lowering medication use, high-density lipoprotein cholesterol, total cholesterol and body mass index.

Outcomes

Cardiovascular events, ESRD and all-cause mortality were ascertained via continuous surveillance of hospitalizations and death certificates, annual telephone follow-up with the participant or a proxy, and linkage with the National Death Index. CHD will be defined as a first occurrence of either adjudicated hospitalization for definite/probable myocardial infarction or death due to CHD. Incident stroke will be defined as a first occurrence of adjudicated hospitalization or death due to definite/probable ischemic stroke. Incident heart failure will be defined as a first occurrence of either hospitalization with a discharge code of 428 in any position for diagnosis using the International Classification of Diseases, 9th Revision (ICD-9) or death due to heart failure, based on a 428 ICD-9 code or an ICD, 10th Revision (ICD-10) code of 150. Incident CKD will be defined as eGFR<60 mL/min/1.73 m² with a ≥25% decline in eGFR since visit 2, or hospitalization due to kidney disease, kidney transplant or dialysis or death due to kidney disease or treated ESRD by USRDS data linkage. For ESRD analyses, the USRDS linkage will be the primary outcome with secondary analyses for kidney failure following Rebholz et al. (Comparison of Cases of Kidney Failure and End-Stage Renal Disease in the Atherosclerosis Risk in Communities Study, submitted for ARIC review).

Fundus photography was conducted during ARIC visit 3 (1993-95) to assess the presence of retinopathy. We will define prevalent retinopathy at visit 3 as a score of ≥20 on the Early Treatment Diabetic Retinopathy Study scale.

Incident diabetes will be defined as self-report of physician diagnosis of diabetes or glucose-lowering medication use measured at visit 3, visit 4 and during the annual telephone follow-up through 2011.
Statistical analyses

We will compare baseline median levels of glycemic markers in blacks and whites, separately in persons with and without diagnosed diabetes at visit 2. We will also calculate the median level of HbA1c, fructosamine, glycated albumin and 1,5-AG within clinical categories of fasting glucose (<100 mg/dL, 100-125 mg/dL and ≥126 mg/dL) and after adjustment for fasting glucose as a continuous variable.

For analyses of retinopathy, we will use logistic regression, since we will consider glycemic markers measured at visit 2 and retinopathy measured at visit 3 to be concurrent. For other outcomes (diabetes, CKD/ESRD, CHD, stroke, heart failure and mortality), we will use Cox proportional hazards regression models. Follow-up will begin at visit 2 and continue through December 31, 2011.

We will first stratify by race and formally compare the magnitude of the hazard ratios for each glycemic marker and outcome using seemingly unrelated estimation. We will then include both black and white participants in the same model with an interaction term between glycemic marker and race, and conduct a formal statistical test of interaction. We will run models with glycemic markers modeled as continuous variables with spline terms to account for non-linear associations with outcomes, as well as categorical variables. Among persons without diagnosed diabetes, we will use diagnostic cut-points recommended by the American Diabetes Association for fasting glucose (<100 mg/dL, 100-125 mg/dL and ≥126 mg/dL for normal, prediabetes and diabetes, respectively) and HbA1c (<5.7%, 5.7-6.4% and ≥6.5% for normal, prediabetes and diabetes, respectively). Since clinical cut-points have not been established for nontraditional markers of hyperglycemia, we will create cut-points that correspond to equivalent percentiles for HbA1c cut-points. We will conduct analogous analyses in persons with diagnosed diabetes. For instance, we will use commonly recommended cut-points for glycemic control using HbA1c (7% or 8%).

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  __X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?  ____ Yes  ____ No

(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?  ____ Yes  __X__ No
8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  
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9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.csc.unc.edu/ARIC/search.php  

| X | Yes | No |

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?  

MSP #2387 – Maruthur et al. - Comparative genetics of fructosamine, glycated albumin, and 1,5-anhydroglucitol in the Atherosclerosis Risk in Communities Study  

Previous relevant publications:  


11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  

| X | Yes | No |

11.b. If yes, is the proposal  

| X | A. primarily the result of an ancillary study (list number* 2009.16) | B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* |  

*ancillary studies are listed by number at http://www.csc.unc.edu/ARIC/forms/  

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.  

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your
responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

REFERENCES


