ARIC Manuscript Proposal # 1587

PC Reviewed: 12/8/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Racial Differences in Glycemic Markers: Implications for Screening and Diagnosis of Diabetes

b. Abbreviated Title (Length 26 characters): Race Differences in Glycemic Markers

2. Writing Group:
Writing group members: Elizabeth Selvin; Mike Steffes; Linda Kao; Christie Ballantyne; Ron Hoogeveen; Josef Coresh, Frederick L. Brancati, others welcome

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

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3. Timeline: Assays have recently been completed. We aim to have this manuscript submitted to the ARIC publications committee in <1 year from the approval date.

4. Rationale:

In January 2010, the American Diabetes Association (ADA) will change the way diabetes is diagnosed. An Expert Panel has recently recommended the use of HbA1c for the diagnosis of diabetes, and the ADA is expected to publish new guidelines incorporating HbA1c as a diagnostic test this January. However, there is on-going debate regarding the interpretation of HbA1c values among African Americans and the use of race-based HbA1c cut-points for diagnosis of diabetes (1-9). African Americans are well known to have higher HbA1c levels than their white counterparts in both the presence and absence of diabetes (1, 3, 10-16) and even in the setting of low glucose levels (12). It is unclear whether this disparity stems from racial differences in post-prandial glycemia (5), the tendency of hemoglobin to undergo glycosylation (4), or differences in screening and diagnostic practices. Serum glycemic markers such as fructosamine, glycated albumin, and 1,5-anhydroglucitol (1,5-AG) offer additional ways to evaluate the implications of racial disparities in glucose homeostasis. HbA1c results from the binding of glucose to hemoglobin in erythrocytes and represents long-term (2-3 month) glycemia. In contrast, fructosamine and glycated albumin are a result of the binding of glucose to serum proteins, and are markers of 2-4 week endogenous glucose exposure. 1,5-AG is a serum marker of glycemic excursions (1,5 AG levels decrease at high levels of glucose).

We will compare HbA1c and fasting glucose to non-traditional glycemic markers in participants in the ARIC CARMRI study to address the question: Do HbA1c levels and other glycemic markers mean the same thing in whites and blacks?

5. Main Hypothesis/Study Questions:

Aim 1: To determine if higher values of HbA1c in blacks are also observed for alternative measures of glycemia.

Hypotheses:

- We will observe higher HbA1c values in blacks as compared to whites after adjustment for fasting glucose
- Glycated albumin and fructosamine are will also be higher in blacks compared to whites after adjustment for fasting glucose
- 1,5-AG will be lower in blacks compared to whites after adjustment for fasting glucose

Racial differences in serum glycemic makers would contradict the notion that HbA1c values are higher in blacks solely as a result of differing characteristics of hemoglobin or red cell turnover as these serum measures are unaffected by hemoglobin or red cell characteristics. 1,5-AG, which is excreted in the urine at high levels of glucose, represents an additional physiological process and can shed light on disparities in glycemia independent of possible racial variation in glycation rates (suggested in prior studies). A comprehensive analysis of alternative glycemic markers might provide independent confirmation of real racial disparities in glycemia (as opposed to mere racial differences in the tendency for hemoglobin to become glycosylated).

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).

Design & Methods

Study population: The study population will be limited to the subsample of ARIC participants for whom a blood sample was obtained at the CARMRI visit (2005-06), the only visit for which data are currently available on serum glycemic markers.

Study design: We will conduct a cross-sectional study of the association of race/ethnicity with glycemic markers (fasting glucose, HbA1c, fructosamine, glycated albumin, and 1,5-AG) among CARMRI participants, stratified by diabetes diagnosis.

Covariates: Age, sex, waist circumference, BMI, total, LDL- and HDL-cholesterol, systolic and diastolic blood pressures, blood pressure medication use, triglycerides, smoking, alcohol consumption, family history of diabetes, physical activity level, education level, dietary intake (FFQ), estimated glomerular filtration rate, and albuminuria.

Exclusions: Persons who are non-white or non-black or missing variables of interest.

Statistical Analysis: We will examine mean levels of glycemic markers stratified by race/ethnicity separately in persons with and without a history of diagnosed diabetes (using information from all previous ARIC visits). We will use linear and logistic regression models to assess the independent association of race/ethnicity with each glycemic marker after adjustment for relevant covariates and glucose levels. We will also examine unadjusted and adjusted levels of serum glycemic markers (glycated albumin, fructosamine, and 1,5-AG) across categories of fasting glucose (<100, 100-<126, >=126 mg/dl) and HbA1c (<5, 5-<5.5, 5.5-6.0, 6.0-6.5, >=6.5%) among persons without a history of diagnosed diabetes. We will test for racial differences in the non-traditional markers after adjustment for fasting glucose. We will test whether race/ethnicity is an independent predictor of discordance between the different glycemic markers. We will test for interactions by gender, BMI, duration of diabetes (in persons with diagnosed diabetes), and the presence of microvascular disease (retinopathy, kidney disease). All analyses will be weighted by the inverse of the sample fractions in the eight sampling strata (four field centers by two IMT groups) using methods for the analysis of complex sample survey design.

We will adjust for standard risk factors measured at the CARMRI visit (cross-sectional design) and also adjustment for cumulative exposure and/or rate of change of exposure using risk factor assessment during the original ARIC Visits, i.e. incorporating repeated measurements occurring prior to the CARMRI visit, beginning in 1987-89.

Limitations: The cross-sectional design and the sample size are major limitations of this study. We have only single measurements of each glycemic marker at a single point in time in CARMRI participants, a small subset of the total ARIC population. We are applying to funding to conduct additional measurements of these markers in the entire cohort and examine prospective associations with clinical outcomes. Thus, in future studies, we will be able to specifically examine the clinical implications of any observed racial differences. And while we will have rigorous measurements of diabetes risk factors, we may not be able to assess the true determinants of any racial differences in glycemic markers in this setting. Nonetheless, we should be able to assess how well these measurements align, if racial disparities are independent of other risk factors, and whether the well-established disparity in HbA1c levels is also observed for other glycemic markers.

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 ICTDER03 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"?
____ Yes ____ No

8.c. If yes, is the author aware that some DNA data is not allowed to be used by 'for profit' groups. Is this data being used by a 'for profit' organization? If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded?
____Yes ____No

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.cscc.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)?

ARIC 59A Correlates of body fat distribution - variation across categories of race, sex and body mass in the Atherosclerosis Risk in Communities Study Duncan, BB
ARIC 90 Race and gender differences in the association of lipoprotein[a] with carotid artery wall thickness: the Atherosclerosis Risk in Communities (ARIC) Study Schreiner, P
ARIC 252 (M) Correlates of prevalent diabetes by race Brancati, FL
ARIC 1451 Race/ethnic differences in diabetes mortality and cardiovascular risk: The Atherosclerosis Risk in Communities (ARIC) Study Selvin, E
12-02-1993
ARIC 167 Incident type 2 diabetes mellitus in a community-based biracial cohort: The Atherosclerosis Risk in Communities Study Brancati, FL
ARIC 251 (M) Racial comparison of physical activity Brancati, FL
ARIC 1011 Stability of haemoglobin A1c (HbA1c) measurements from frozen whole blood samples stored for over a decade. Selvin, E
ARIC 657 Sensitivity and specificity of anthropometrics for the predi ction of diabetes in a biracial cohort Stevens, J
ARIC 1024 Glycemic control and coronary heart disease risk in persons with and without diabetes: The Atherosclerosis Risk in Communities Study Selvin, E
ARIC 1025 Glycemic control, Atherosclerosis, and risk factors for cardiovascular disease in individuals with diabetes: The ARIC Study Selvin, E
ARIC 1056 HbA1c and peripheral arterial disease in diabetes Selvin, E
ARIC 1067 Glycemia (haemoglobin A1c) and incident stroke: The ARIC Study Selvin, E
ARIC 1164 Hemoglobin A1c as a Risk Factor for Heart Failure Hospitalization among Persons with Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study Pazin Filho, A
ARIC 1418 Glycemic control (hemoglobin A1c), cognitive decline and dementia risk: The Atherosclerosis Risk in Communities (ARIC) Study Selvin, E
ARIC 1431 Hemoglobin A1c, glucose, and incident diabetes: the Atherosclerosis Risk in Communities Study
1496 Measurement of Hemoglobin A1c (HbA1c) from Stored Whole Blood Samples in the Atherosclerosis Risk in Communities Study Selvin, E
ARIC 1488 The association of hemoglobin A1c with incident heart failure among persons without diabetes: The Atherosclerosis Risk in Communities (ARIC) Study Matsushita, KM
1245 Glycemic Control (HbA1c) and Incident Chronic Kidney Disease in Diabetes: The Atherosclerosis Risk in Communities Study Bash, LD

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.cscc.unc.edu/aric/forms/

12. 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. ES

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