

ARIC Manuscript Proposal #2110

PC Reviewed: 4/9/13
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title:

Comparative associations of diabetes risk factors with five measures of hyperglycemia

b. Abbreviated Title (Length 26 characters): Comparing glyceemic markers

2. Writing Group:

Writing group members: Anna Poon; Julie Bower, PhD, MPH; Stephen Juraschek; Christie Ballantyne, MD; Michael Steffes, MD, PhD; Elizabeth Selvin, PhD, MPH; others welcome

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

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3. Timeline: We intend to complete this manuscript within 6 months of approval

4. Rationale:

Fasting glucose and hemoglobin A1c are the standard measures used for diagnosis and management of diabetes in clinical practice (American Diabetes Association 2013). Recently, nontraditional markers of glycemia, including 1,5-anhydroglucitol (1,5-AG), fructosamine, and glycated albumin, have shown promise in predicting diabetes risk (Juraschek, et al. 2012) and clinical outcomes (Selvin, Francis, et al. 2011). There is growing interest in the use of these alternative markers of hyperglycemia in settings where short-term glycemic control is of interest and/or where traditional measures might not perform optimally (Rubinow and Hirsch 2011). However, before these markers can be adopted in widespread practice, additional information is needed to understand how diabetes risk factors may affect these nontraditional markers and whether any associations are similar to or different from standard markers of hyperglycemia.

Our analysis will be a comparative study of the differential associations of traditional and nontraditional glycemic markers with diabetes risk factors.

5. Main Hypothesis/Study Questions:

Hypothesis: Nontraditional glycemic markers may be associated with diabetes through a pathway different from traditional glycemic markers. The comparative association of nontraditional and traditional markers with diabetes risk factors may therefore not be consistent. Associations with diabetes risk factors are expected to differ in terms of magnitude and effect.

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 population. The study population will include all participants from the 2005-2006 ARIC CARMRI substudy (Wagenknecht, et al. 2009). Glycated albumin, fructosamine, and 1,5-AG were measured from stored serum samples in all CARMRI participants in 2009 as a part of Ancillary Study 2009.16.

Exclusions. Participants missing measurements for serum glycemic markers and other variables of interest will be excluded from this analysis.

Study design. The study design is cross-sectional. Participants are a weighted probability sample of ARIC visit 4 participants. All variables considered in this study were measured at the CARMRI visit.

Exposure variables. Diabetes risk factors to be examined will include age, race, gender, family history of diabetes, C-reactive protein (CRP), and measures of adiposity defined by body mass index (BMI), waist-hip ratio (WHR), and waist circumference (WC). CRP concentrations were measured using an immunoturbidimetric assay implemented on a Roche Hitachi 717 Analyzer (ARIC Carotid MRI Study Investigators 2005). Height, weight, and waist and hip circumference were measured during the study visit (ARIC Carotid MRI Study Investigators, 2005)

Outcome variables. Outcome variables include glycated albumin, fructosamine, 1,5-AG, hemoglobin A1c, and fasting glucose. Hemoglobin A1c was measured using a Tina-quant II

immunoassay method (Roche Diagnostics, Basel, Switzerland) and calibrated to the Diabetes Control and Complications Trial assay. Glucose was measured in serum using the hexokinase method (Roche Diagnostics). Both hemoglobin A1c and fasting glucose were measured in 2005-2006 using a Roche Hitachi 911 Analyzer. Fructosamine (Roche Diagnostics), glycated albumin (Lucica GA-L; Asahi Kasei Pharma Corporation, Tokyo Japan), and 1,5-AG (GlycoMark, Winston-Salem, NC) were measured in 2009 using a Roche Module P800 system (Roche Diagnostics).

Covariates. Covariates will include hypertension (SBP/DBP \geq 140/90mmHg), smoking status (current, former, never; pack years), low HDL (<40 mg/dL for men and <50 mg/dL for women), high triglycerides (>150 mg/dL), albuminuria (urine albumin-creatinine ratio \geq 30mg/g), reduced kidney function (eGFR<60 mL/min/1.73m², using CKD-EPI equation), and serum albumin (g/dL). We will also consider the impact of statin use on the associations of diabetes risk factors, particularly CRP, with each of the glycemic markers.

Statistical analysis

Exploratory analyses. Summary statistics, histograms, and box-and-whisker plots will be used to describe the distributions of traditional and nontraditional glycemic markers overall.

Baseline characteristics. Baseline covariates will be summarized by quartiles of each glycemic marker (**table 1a**). Associations between baseline covariates with glycemic marker levels will be evaluated using ANOVA for continuous variables and chi-squared test for categorical variables. In a sensitivity analysis, characteristics for excluded participants will be summarized to confirm that they are missing completely at random (**table 1b**).

Modeling. Simple regression will be used to evaluate the continuous association of glycemic markers with diabetes risk factors. Models will be nested to examine unadjusted and adjusted relationships. Models will include minimal adjustment for demographics characteristics, and full adjustment for clinical characteristics (**table 2**). Logistic regression will be used to evaluate the association of hyperglycemia with diabetes risk factors (**table 3**). Hyperglycemia will be defined using two cutoffs. For fasting glucose, hemoglobin A1c, glycated albumin, and fructosamine, hyperglycemia will be evaluated separately for persons at or above the 75th and 90th percentile. For 1,5-AG, hyperglycemia will be evaluated separately for persons at or below the 10th and 25th percentiles due to its inverse association with glycemia. Models will be fully adjusted for demographic and clinical characteristics. Fructosamine models will be additionally adjusted for serum albumin because levels of this serum protein may affect fructosamine assays. Associations of glycemic markers with diabetes risk factors will be compared by percentiles. Analyses will be repeated adjusting separately for reduced kidney function, albuminuria, BMI, WHR, and WC. All of the above analyses will be weighted to accommodate the complex sample survey design and for variance estimation.

Limitations. The analytic sample is limited because the CARMRI participants are a small subsample of the larger ARIC cohort. Repeated measurements for serum biomarkers are not available.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes 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 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

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> 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)?

1. Juraschek, SP, MW Steffes, ERM III Miller, and E Selvin. "Alternative Markers of Hyperglycemia and Risk of Diabetes." *Diabetes Care* 35, no. 11 (2012): 2265-2270.

2. Selvin, E, et al. "Nontraditional markers of glycemia: associations with microvascular conditions." *Diabetes Care* 34, no. 4 (Apr 2011): 960-7.

3. Selvin, E, MW Steffes, CM Ballantyne, RC Hoogeveen, J Coresh, and FL Brancati. "Racial differences in glycemc markers: a cross-sectional analysis of community-based data." *Annals of Internal Medicine* 154, no. 5 (March 2011): 303-309.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes No

11.b. If yes, is the proposal

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.csc.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.

Works Cited

American Diabetes Association. "Standards of medical care in diabetes--2013." *Diabetes Care* 36 (Jan 2013): S11-S66.

ARIC Carotid MRI Study Investigators. *Manual 1: Description and Study Management*. Manual, Department of Biostatistics (CSCC), Atherosclerosis Risk in Communities Carotid MRI Study, Chapel Hill: ARIC Coordinating Center, 2005, 1-13.

ARIC Carotid MRI Study Investigators. *Manual 5: Lipid and Lipoprotein Determinations*. Manual, Department of Biostatistics (CSCC), Atherosclerosis Risk in Communities Carotid MRI Study, Chapel Hill: ARIC Coordinating Center, 2005, 1-67.

Juraschek, SP, MW Steffes, ERM III Miller, and E Selvin. "Alternative Markers of Hyperglycemia and Risk of Diabetes." *Diabetes Care* 35, no. 11 (2012): 2265-2270.

Rubinow, KB, and IB Hirsch. "Reexamining Metrics for Glucose Control." *The Journal of the American Medical Association* 305, no. 11 (March 2011): 1132-1133.

Selvin, E, et al. "Nontraditional markers of glycemia: associations with microvascular conditions." *Diabetes Care* 34, no. 4 (Apr 2011): 960-7.

Selvin, E, MW Steffes, CM Ballantyne, RC Hoogeveen, J Coresh, and FL Brancati. "Racial differences in glycemic markers: a cross-sectional analysis of community-based data." *Annals of Internal Medicine* 154, no. 5 (March 2011): 303-309.

Wagenknecht, L, et al. "Correlates of carotid plaque presence and composition as measured by MRI: the Atherosclerosis Risk in Communities Study." *Circulation: Cardiovascular Imaging* 2, no. 4 (July 2009): 314-322.