ARIC Manuscript Proposal # 1588

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

1.a. Full Title:

Non-traditional Markers of Glycemia: Associations with Micro- and Macrovascular Disease

b. Abbreviated Title (Length 26 characters): Glycemic Markers and Disease

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

HbA1c is the gold-standard measure for assessment of long-term (2-3 month) glycemic control. Nonetheless, measurement of HbA1c requires whole blood and relatively labor-intensive assay methodologies. Serum glycemic markers such as fructosamine, glycated albumin, and 1,5-anhydroglucitol (1,5-AG) have been proposed to have clinical utility for use in conjunction with fasting glucose and HbA1c for diagnosis and management of diabetes. Glycated albumin, fructosamine, and 1,5-AG are short-term markers of glycemia and 1,5-AG reflects glycemic excursions. The assay for 1,5-AG is approved and marketed for clinical use in the U.S. and is covered by Medicare. The glycated albumin assay under investigation here is widely used in Japan to monitor short-term glycemic control but is not yet approved for clinical use in the U.S. (poised to receive FDA approval soon). The relationship between fasting glucose and HbA1c and retinopathy is well established (1-3) and previous epidemiologic studies have shown moderate cross-sectional and prospective associations between fasting glucose and HbA1c and measures of cardiovascular disease (4-8). However, the epidemiology of serum glycemic markers is largely uncharacterized and few head-to-head comparisons have been conducted. Physicians typically use multiple measures to assess metabolic status of their patients and because these markers represent different aspects of glycemia, there is potential for them to add to our understanding of the role of glycemia in the development of disease. The aim of this study is to assess the relationship of non-traditional and standard glycemic markers to common microvascular and macrovascular complications in a general population. To accomplish this aim, we will conduct a comprehensive assessment of the epidemiologic associations of fasting glucose, HbA1c, fructosamine, glycated albumin, and 1,5-AG with measures of clinical and subclinical microvascular and macrovascular disease available from participants who attended the ARIC CARMRI visit.

5. Main Hypothesis/Study Questions:

Aim 1: To characterize the cross-sectional associations of non-traditional glycemic markers—fructosamine, glycated albumin, and 1,5-AG—with measures of microvascular and macrovascular disease and compare these associations to those observed for standard glycemic measures (fasting glucose, HbA1c).

Hypothesis 1: Standard (glucose and HbA1c) and non-traditional markers (glycated albumin, fructosamine) will be similarly and positively associated with a history of clinical CVD and subclinical measures of CVD in persons with and without a history of diabetes. 1,5-anhydroglucitol may be inversely associated with measures of CVD in persons with and without a history of diabetes.

Hypothesis 2: 1,5-AG will be independently and inversely associated with measures of kidney function and kidney damage in persons with and without diabetes. The other glycemic markers will only be independently associated with measures of kidney disease and function in persons with a history of diabetes or at high ("diabetic"/undiagnosed diabetes) levels of the respective markers (threshold effect).

Hypothesis 3: HbA1c, glucose, fructosamine, and 1,5-AG will be positively associated with retinopathy, but only at high ("diabetic") levels of these markers.

1,5-AG will be negatively associated with retinopathy at very low levels (threshold 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).

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 glycemic markers (fasting glucose, HbA1c, fructosamine, glycated albumin, and 1,5-AG) with measures of microvascular and macrovascular disease in CARMRI participants, stratified by diabetes diagnosis.

Exposures: fasting glucose, HbA1c, fructosamine, glycated albumin, and 1,5-anhydroglucitol. Exposures will be categorized into quartiles. We will consider expressing all measures to 1-SD change for comparability and possibly converting fructosamine and glycated albumin into "HbA1c-equivalent" units for comparative purposes. We will also examine clinically relevant categories of HbA1c (<5, 5-<5.5, 5.5-<6, 6-<6.5, >=6.5%) and glucose (<100, 100-<126, >=126 mg/dl).

Outcomes:

- *Subclinical cardiovascular disease*: Average internal carotid intima-media wall thickness (IMT), carotid artery volume, and plaque presence via MRI.
- *Clinical cardiovascular disease*: self-reported cardiovascular disease (CHD or stroke) history at CARMRI, any prior visit or an adjudicated (non-fatal) clinical event or silent MI prior to the date of the CARMRI visit, or silent MI detected at the CARMRI visit.
- *Retinopathy*: Retinal photographic data are available for all participants at the CARMRI visit. Trained graders evaluated retinal photographic slides for focal lesions, including signs typical of diabetic retinopathy, including both background and proliferative retinopathy (e.g., microaneurysms, retinal hemorrhages, hard exudates and/or cotton wool spots) according to a standardized protocol. The main retinal outcome of interest will be any retinopathy at the CARMRI visit in the absence of other retinal vascular causes, e.g., retinal vein occlusion. Secondary analyses will be conducted to examine the associations of glycemic markers with specific retinal findings and disease severity. Because retinal data were also collected at Visit 3 (1993-95) we may incorporate these data to distinguish cases of longer duration from those newly detected at the CARMRI visit.
- *Kidney disease*: We will define incident kidney disease based on an glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 estimated from serum creatinine

measured at the CARMRI visit, an incident hospitalization (discharge) coded for chronic renal disease (ICD-9 codes 581-583 or 585-588), hypertensive renal disease (ICD-9 code 403), hypertensive heart and renal disease (ICD-9 code 404), unspecified disorder of kidney and ureter (ICD-9 code 593.9), diabetes with renal manifestations (ICD-9 code 250.4), kidney transplantation, renal dialysis, or adjustment/fitting of catheter (ICD-9 codes V42.0, V45.1, or V56), hemodialysis (ICD-9 code 39.95) or peritoneal dialysis (ICD-9 code 54.98), without acute renal failure (ICD-9 codes 584, 586, 788.9, or 958.5) as the primary or secondary hospitalization code prior to the CARMRI visit. We will define albuminuria as an albumin to creatinine ratio of 30 mg/g or greater (which includes both the categories of microalbuminuria and macroalbuminuria). We will also separately estimate GFR based on serum cysatin C from the CARMRI visit.

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, and dietary intake (FFQ).

Potential effect modifiers: we will test for effect modification by age, categories of body mass index, and race/ethnicity

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

Statistical Analysis: We will use multivariable (linear and logistic) regression models to assess the independent association of each glycemic marker with the above-listed outcomes after adjustment for relevant covariates among persons with and without a history of diagnosed diabetes. We will test for interactions by age, race/ethnicity, and body mass index categories. 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.

Threshold effects: We will implement linear and restricted cubic splines in our logistic and linear models to characterize possible non-linear relationships or threshold effects.

History of diagnosed diabetes: We will initially conduct analyses stratified by diagnosed diabetes status (incorporating information on self-reported physical diagnosis of diabetes and diabetes medication use from the previous visits), but we will consider conducting additional analyses modeling each glycemic marker according to diabetes-specific categories to show any associations across the entire spectrum of glucose homeostasis.

Incorporating data from the prior visits: 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 limited sample size and cross-sectional design 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. Pending funding, we plan to conduct addition measurements of these markers in the entire cohort and examine prospective associations with clinical outcomes. Thus, in future studies, we will be able to rigorously characterize any prospective associations between non-traditional glycemic markers and clinical outcomes.

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)?

2004.11-CARMRI 1211 Determinants of carotid plaque presence and pathology as measured by magnetic resonance imaging: The ARIC Study Wagenknecht, LE

2004.11-CARMRI 1215 Association of chronic kidney disease with carotid artery plaque characteristics Coresh, J
2004.11-CARMRI 1241 Prevalence, Methods and Reliability in the Multi-center Atherosclerosis Risk in Communities Carotid MRI Study Wasserman, BAW
337A Retinopathy in persons without diabetes in the ARIC study Klein, R
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

References:

1. The International Expert C. International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes. Diabetes Care. 2009.
2. McCane DR, Hanson RL, Charles MA, Jacobsson LTH, Pettitt DD, Bennett PH, et al. Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. BMJ. 1994;308(6940):1323-8.
3. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes. 1995;44(8):968-83.
4. Selvin E, Coresh J, Golden SH, Boland LL, Brancati FL, Steffes MW. Glycemic Control, Atherosclerosis, and Risk Factors for Cardiovascular Disease in Individuals With Diabetes: The Atherosclerosis Risk in Communities study. Diabetes Care. 2005;28(8):1965-73.
5. Selvin E, Coresh J, Golden SH, Brancati FL, Folsom AR, Steffes MW. Glycemic Control and Coronary Heart Disease Risk in Persons With and Without Diabetes: The Atherosclerosis Risk in Communities Study. Archives of Internal Medicine. 2005;165(16):1910-6.
6. Selvin E, Coresh J, Shahar E, Zhang L, Steffes M, Sharrett AR. Glycaemia (haemoglobin A1c) and incident ischaemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. The Lancet Neurology. 2005;4(12):821-6.
7. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Annals of Internal Medicine. 2004;141(6):413-20.
8. Meigs JB, Singer DE, Sullivan LM, Dukes KA, D'Agostino RB, Nathan DM, et al. Metabolic control and prevalent cardiovascular disease in non-insulin-dependent diabetes mellitus (NIDDM): The NIDDM Patient Outcome Research Team. Am J Med. 1997;102(1):38-47.