

ARIC Manuscript Proposal #2500

PC Reviewed: 2/10/15
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Performance of Nontraditional Glycemic Markers in Older Adults with Chronic Kidney Disease

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

2. Writing Group:

Yuenting Diana Kwong, MD, Tariq Shafi, MD; Natalie Daya, Stephen Juraschek, MD, PhD, Josef Coresh, MD, PhD, Elizabeth Selvin, MHS, PhD, Morgan Grams MD, PhD, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. YDK [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:

Data analysis will start immediately. A manuscript is expected to be prepared within 6 months.

4. Rationale:

Hemoglobin A1c (HbA1c) is one of the most widely used values to determine glycemic control in patients with diabetes. HbA1c reflects previous 2-3 months of glycemic control as the value is dependent on the process of glucose binding to hemoglobin during the ~120 day life span of a red blood cell. However, there are questions concerning the validity of hemoglobin A1c for diagnosing and managing diabetes in the setting of chronic kidney disease (CKD). In CKD, red blood cell survival has been reported to decrease by 20-70%, which could affect the validity of

the HbA1c test.¹ Most studies have indicated that HbA1c is falsely lowered^{2,3} and may not directly correlate⁴ to ambient blood glucoses in patients with CKD.

Markers such as glycosylated proteins (specifically glycosylated albumin and fructosamine) as well as 1,5-anhydroglucitol (AG) have been proposed as alternative measures of glycemic control in patients in which the HbA1c test is inaccurate.⁵ However, there are limited data on the performance of these markers, particularly in older patients with milder forms of CKD, a subgroup particularly prevalent among persons with diabetes. Hypoalbuminemia is often very common among the elderly with CKD secondary to malnutrition. The performance of glycosylated proteins and HbA1c in older adults with and without CKD is also unknown.

We propose to assess the association of traditional (HbA1c, fasting glucose) and nontraditional glycemic markers (fructosamine, glycosylated albumin, and 1,5-AG) at different stages of chronic kidney disease (defined by estimated glomerular filtration rate and albuminuria) in the ARIC Study population at visit 5 (2011-2013) with careful attention to possible confounding by albumin level. We will also stratify by anemia and age to determine performance in particular population subgroups.

5. Main Hypothesis/Study Questions:

1. Do the correlations between glycemic markers (HbA1c; 1,5 anhydroglucitol; fructosamine; glycosylated albumin) and fasting glucose differ by CKD stage in an older population?
2. Do the correlations between glycemic markers and fasting glucose differ by level of hemoglobin in an older population? Is this independent of CKD status?

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: Cross sectional study design of visit 5. If enough events occur after visit 5, we will also evaluate the prospective associations of glycemic markers, vascular events, and mortality.

Inclusion/exclusion: ARIC participants at visit 5 NOT on dialysis. Visit 5 was used as the baseline visit because the population is older and this was the first visit with all of the following

¹ Loge J., Lange R., and Moore C.: Characterization of the anemia associated with chronic renal insufficiency. *Am J Med* 1958; 24: pp. 4-18

² Chen HS, Wu TE, Lin HD, Jap TS, Hsiao LC, Lee SH, et al. Hemoglobin A(1c) and fructosamine for assessing glycemic control in diabetic patients with CKD stages 3 and 4. *Am J Kidney Dis* 2010; May;55(5):867-74.

³ Freedman BI, Shihabi ZK, Andries L, Cardona CY, Peacock TP, Byers JR, et al. Relationship between assays of glycemia in diabetic subjects with advanced chronic kidney disease. *Am J Nephrol* 2010;31(5):375-9.

⁴ Vos FE, Schollum JB, Coulter CV, Manning PJ, Duffull SB, Walker RJ. Assessment of markers of glycaemic control in diabetic patients with chronic kidney disease using continuous glucose monitoring. *Nephrology (Carlton)* 2012; Feb;17(2):182-8.

⁵ Parinello CM, Selvin E. Beyond HbA1c and Glucose: the Role of Nontraditional Glycemic Markers in Diabetes Diagnosis, Prognosis and Management. *Curr Diab Rep* 2014; 14:548

values: A1c, ACR, 1,5 anhydroglucitol, fructosamine and glycated albumin. Participants on missing data on any of the markers and/or the covariates listed will be excluded.

Exposures: A1c, 1,5 anhydroglucitol, fructosamine and glycated albumin

Covariates: Age, sex, race, hemoglobin, serum albumin, urine albumin-to-creatinine ratio

Outcome: association with fasting glucose and if available, vascular events and mortality

Data analysis:

We will assess distribution of hyperglycemic indices by CKD stages (GFR and albuminuria) in subgroups of persons with and without diabetes. We will assess the continuous cross-sectional relationship between eGFR and each glycemic marker using piece-wise linear splines. Similarly, we will examine the relationship between continuous ACR and each glycemic marker. We will use linear regression to assess whether the association of different measures of hyperglycemia with fasting glucose varies by CKD stage by testing an interaction term. If available, we then will assess the relationship of each marker by CKD staging to vascular events and mortality using Cox proportional hazards regression.

Limitations:

1. We only have single measurements of each glycemic marker and single fasting glucose values. Single fasting glucose values may be highly variable based on study subject and may not reflect ambient hyperglycemia.
2. Because the cross sectional visit is done at visit 5, we have limited data on how each marker will predict health outcomes of our study population. If available, we will assess subsequent vascular events and mortality as it relates to glycemic marker indices by CKD staging (no CKD, CKD Stages G1-G5, and CKD Stages A1-A3).

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)?

Juraschek SP, Steffes MW, and Selvin E. Associations of Alternative Markers of Glycemia with Hemoglobin A1c and Fasting Glucose. *Clinical Chemistry* 58:12. 1648-1655 (2012).

Selvin E et al. Nontraditional Markers of Glycemia: Associations with microvascular conditions. *Diabetes Care* 34:960-967, 2011.

Selvin et al. Association of 1,5 Anhydroglucitol with Diabetes and Microvascular Conditions. *Clinical Chemistry* 60: 11.

Selvin et al. Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: A prospective cohort analysis of ARIC study. *Lancet*. 2014

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* 2011.03)**
 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.