ARIC Manuscript Proposal #2114

PC Reviewed: 4/9/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Prognostic utility of fructosamine and glycated albumin for incident diabetes and microvascular complications

b. Abbreviated Title (Length 26 characters): Fructosamine and glycated albumin

2. Writing Group:

Writing group members: Elizabeth Selvin; Andreea Rawlings; Frederick L Brancati; Ronald Klein; Richey Sharrett; Michael Steffes; 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: We aim to submit this paper for ARIC review <1 year from approval of the manuscript proposal

4. Rationale:

Hemoglobin A1c (HbA1c) results from the glycation of hemoglobin in erythrocytes and represents long-term (2-3 month) glycemia. For decades, HbA1c has long been the primary test used to monitor glycemic control and guide treatment of diabetes in clinical practice. In a major change to clinical guidelines in 2010, HbA1c was recommended for use as a diagnostic test for diabetes (1). In addition to its central role in monitoring glycemic control, HbA1c is now being widely adopted as the first-line test for screening and diagnosis of diabetes. The epidemiologic evidence supporting current recommendations for use of HbA1c for screening and diagnosis comes primarily from studies that have characterized the association of HbA1c with prevalent retinopathy (2-6).

Fructosamine and glycated albumin are markers of short-term (2-4 week) glycemic control that may add complementary information to HbA1c for the identification of persons at risk for the development of diabetes and its complications (7-10). Fructosamine and glycated albumin are independent of both erythrocyte and hemoglobin characteristics; they reflect the modification of serum proteins (mainly albumin), which have a faster turnover (~10-14 days) as compared to erythrocytes (~120 days). Glycated albumin may be superior to fructosamine for prediction of outcomes since it is a measure of the ratio of glycated albumin to total serum albumin. The fructosamine assay measures total glycated serum proteins and is not corrected for circulating serum protein concentrations, which can fluctuate due to acute illness or other inflammatory states, liver disease and nutritional status.

Fructosamine is FDA-approved for clinical use, but is not routinely used in the U.S. The lack of evidence connecting fructosamine to long-term outcomes has been cited as a major barrier to its use and interpretation, especially compared to HbA1c (11). A glycated albumin assay has been developed (Asahi Kasei Corporation) but is not FDA-approved for clinical use in the U.S., although it is widely used in Japan and China for monitoring short-term glycemic control in persons with diabetes.

5. Main Hypothesis/Study Questions:

The overarching objective of this study is to characterize the associations of fructosamine and glycated albumin with incident diabetes, retinopathy, and chronic kidney disease in the community-based ARIC Study. We will compare fructosamine and glycated albumin to HbA1c for the identification of persons who are at high risk for diabetes-related complications.

Hypothesis 1: Fructosamine and glycated albumin will be potent risk factors for the development of diabetes (in persons without diabetes at baseline), retinopathy, and kidney disease among before and after adjustment for potential confounding factors.

Hypothesis 2: Fructosamine and glycated albumin will add independent prognostic information over and above A1C for the prediction of retinopathy and kidney disease in persons with and without diabetes.

Hypothesis 3: Glycated albumin will be more strongly associated with outcomes and a better marker of prognosis compared to fructosamine.

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: Prospective cohort analysis with visit 2 (1990-1992) as baseline

Exposures: Glycated albumin and fructosamine measured in 2012-2013 at the University of Minnesota as part of Dr. Selvin's ancillary study from stored serum samples originally collected at visit 2 (1990-1992).

Exposures (for comparison): HbA1c and fasting glucose

Outcomes: incident diabetes (visit-based and post-visit 4 self-reported cases), incident kidney disease, and prevalent retinopathy (assessed at visit 3 and a subsample of participants at visit 4). We will also examine incident retinopathy in the subsample of participants who did not have retinopathy at visit 3 but developed it by visit 4.

Incident diabetes: we will use two definitions of diabetes, a visit-based definition and an interview-based definition. Visit based diabetes will be defined based on serum glucose measurements, a self-reported diagnosis of diabetes, or medication use at the subsequent two ARIC visits (~6 years of follow-up) (12). Interview-based diabetes will be defined on the basis of a self-reported diabetes diagnosis or diabetes medication use during the ARIC visits and subsequent annual follow-up telephone calls.

Incident chronic kidney disease: We will define incident chronic kidney disease using established definitions in the ARIC Study (13). Specifically, we will define incident chronic kidney disease as a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 estimated from serum creatinine measured at visit 4 (1996 –1998), visit 5 (2011-2013), or a kidney disease hospitalization or death identified by continuous active surveillance. End-stage renal disease (ESRD) is comprised of the subset of hospitalizations indicating kidney transplant or dialysis (14). We will conduct sensitivity analyses to compare definitions based on estimated glomerular filtration rate, a creatinine rise, hospitalization for kidney disease, or combinations of the aforementioned events.

Prevalent retinopathy: We will define prevalent retinopathy based on retinal photographs taken at visit 3 (1993–1995) following a standardized protocol that has been previously documented (15, 16). Briefly, after 5 min of dark adaptation, a nonmydriatic 45-degree retinal photograph centered on the optic disc and macula was taken of one randomly selected eye. Trained readers masked to participant information evaluated each of the photographs. We will define any retinopathy as a severity score of 14 or higher according to a modification of the Airlie House classification system, as used in the Early Treatment Diabetic Retinopathy Study

(ETDRS) (15, 17). A retinopathy severity score was assigned on the basis of the presence of lesions and classified as follows: none (ETDRS <14), mild retinopathy (ETDRS 14–20), or moderate to severe retinopathy (ETDRS 35) (18). Mild retinopathy usually consists of one or two microaneurysms or small hemorrhages; moderate or severe retinopathy consists of both microaneurysms and hemorrhages, often accompanied by hard or soft exudates, intraretinal microvascular abnormalities, venous beading, or less commonly vascular proliferative changes.

Incident retinopathy: A repeat retinal examination was conducted in a subset of participants at visit 4 in the same eye using the identical protocol. Incident retinopathy will be defined as an ETDRS score 14 at visit 4 among individuals who were free of retinopathy at visit 3.

Exclusions: Missing information on exposures or covariates of interest, race other than white or black, and blacks in the Minneapolis and Washington County cohorts. Persons who are non-fasting will be excluded from comparative analyses of fasting glucose. For analyses of kidney outcomes, we will exclude participants with a history of kidney disease. For analyses of prevalent retinopathy, we will exclude persons who did not attend visit 3 (at which retinal examinations were conducted), who did not receive a retinal examination, or who had retinal photographs that were not in the same eye or un-gradable.

Stratification: We will conduct analyses stratified by history of diagnosed diabetes based on self-reported physician diagnosis or diabetes medication use at or before visit 2.

Subgroups: We will specifically examine the associations of fructosamine and glycated albumin with outcomes in subgroups of persons in the pre-diabetic range of A1c (5.7% to 6.4%) and fasting glucose (100 mg/dL to 125 mg/dL), among persons without anemia (anemia will be defined as hemoglobin <13 g/dL in men; hemoglobin <12 g/dL in women)(19), and also among persons with and without chronic kidney disease (estimated GFR <60 ml/min/1.73 m^2) at baseline and among the small subgroups of persons with more severely reduced kidney function (recognizing the power will be quite low in this small subgroup) (for non-CKD outcomes). Persons with anemia and kidney disease are subpopulations in in which performance of A1C is thought to be problematic (20, 21).

Statistical analyses: We will estimate hazard ratios and their 95% confidence intervals using Cox proportional hazards models. The proportional hazards assumption will be examined using log-(-log) plots and by testing risk factor-by-time interactions; if the assumption is violated the interactions term(s) will be kept in the model and the time-dependent nature of the risk will be interpreted accordingly. For analyses of prevalent retinopathy, we will use logistic regression. We will consider the following core models:

Model 1: age, sex, race-center.
Model 2: age, sex, race-center, low-density and high-density cholesterol levels, triglyceride level, body mass index, waist-to-hip ratio, systolic blood pressure, hypertension medication use, family history of diabetes, education level (visit 1), alcohol use, physical activity (visit 1), and smoking status.

Model 3: all variables in Model 2 + HbA1c (per %-point)
Model 4: all variables in Model 2 + fasting glucose (per mg/dL)

We will model fructosamine and glycated albumin in diabetes-specific quartiles and also continuously. To characterize the continuous associations, we will generate piece-wise linear splines with knots corresponding to the cutoffs for the quartiles and we will also implement restricted cubic splines to obtain a smoother fit to the data. Model discrimination will be assessed using Harrell's C statistic. We will test for interactions by race. To evaluate the overall improvement in risk classification for the addition of fructosamine or glycated albumin to the fully adjusted model including HbA1c, we will calculate the net-reclassification improvement statistic (NRI) and the integrated-discrimination improvement statistic (IDI) (22).

Sensitivity analyses: There is ongoing debate regarding the need for correction of fructosamine assays for serum albumin concentrations (23, 24). Thus, we will also conduct additional analyses with further adjustment for total serum albumin. We will conduct sensitivity analyses excluding persons with a history of diagnosed or undiagnosed diabetes (based on HbA1c ≥6.5% or fasting glucose ≥126 mg/dL). As mentioned above, we will also conduct sensitivity analyses comparing different definitions of incident kidney disease.

Limitations:

- Reliance on single measurements of fructosamine and glycated albumin at baseline.
- A limited number of fasting glucose measurements during the follow-up period (two follow-up visits) to define incident diabetes.
- Lack of validation of self-reported diabetes cases during the annual follow-up telephone calls.
- Retinal photograms were taken in only one eye, which may result in low sensitivity for the detection of retinopathy, leading to misclassification of cases as non-cases.
- The retinal examination in all ARIC participants was conducted at visit 3 and the exposures of interest in this paper are only available at visit 2 (three years earlier).
- The second retinal examination (visit 4) was conducted in only a subsample of participants, severely limiting our power for analyses of incident retinopathy. Furthermore, prior studies have shown "disappearance" of retinal signs as well as "incidence". This suggests the potential for misclassification of retinopathy at follow-up and that not all incidence may be truly "new."
- We also only have serum creatinine measurements during one subsequent visit for the detection of decreased kidney function.
- As with all observational studies, we will not be able to eliminate the possibility of residual confounding despite rigorous adjustment for known risk factors.

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"?
____ 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)?

Associations of alternative markers of glycemia with hemoglobin A(1c) and fasting glucose. Juraschek SP, Steffes MW, Selvin E. Clin Chem. 2012 Dec;58(12):1648-55. doi: 10.1373/clinchem.2012.188367. Epub 2012 Sep 27. PMID: 23019309

Alternative markers of hyperglycemia and risk of diabetes. Juraschek SP, Steffes MW, Miller ER 3rd, Selvin E. Diabetes Care. 2012 Nov;35(11):2265-70. doi: 10.2337/dc12-0787. Epub 2012 Aug 8. PMID: 22875225

Racial differences in glycemic markers: a cross-sectional analysis of community-based data. Selvin E, Steffes MW, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL. Ann Intern Med. 2011 Mar 1;154(5):303-9. PMID: 21357907

Nontraditional markers of glycemia: associations with microvascular conditions. Selvin E, Francis LM, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL, Steffes MW. Diabetes Care. 2011 Apr;34(4):960-7. doi: 10.2337/dc10-1945. Epub 2011 Feb 18. PMID: 21335368

Glycated hemoglobin and the risk of kidney disease and retinopathy in adults with and without diabetes. Selvin E, Ning Y, Steffes MW, Bash LD, Klein R, Wong TY, Astor

BC, Sharrett AR, Brancati FL, Coresh J. Diabetes. 2011 Jan;60(1):298-305. doi: 10.2337/db10-1198. Epub 2010 Oct 26. PMID: 20978092

Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. N Engl J Med. 2010 Mar 4;362(9):800-11. doi: 10.1056/NEJMoa0908359. PMID: 20200384

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/

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.

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