ARIC Manuscript Proposal #2795

PC Reviewed: 7/12/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Normal ranges for fructosamine, glycated albumin, and 1,5-anhydroglucitol in a community-based population

b. Abbreviated Title (Length 26 characters): Normal values for glycemic markers

2. Writing Group:
Writing group members: Elizabeth Selvin; Menglu Liang; David Sacks; Amy Saenger; 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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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: All data are in hand. We anticipate <6 month timeline from time of MSP approval to submission of the manuscript for publication.

4. Rationale: There is growing interest in non-traditional biomarkers of hyperglycemia such as fructosamine, glycated albumin and 1,5-anhydroglucitol (1,5-AG), particularly for use in settings where traditional measures (glucose and HbA1c) are problematic or where intermediate (2-4 week) glycemic control is of interest. A barrier to the use of

nontraditional tests of hyperglycemia is that their reference ranges and 'normal' values are not well established.

5. Main Hypothesis/Study Questions: The objective of this study is to determine reference intervals and evaluate demographic differences in the normal values of 1,5-AG, fructosamine, and glycated albumin using data from the community-based Atherosclerosis Risk in Communities (ARIC) Study.

Previous studies examining the reference ranges and potential clinical cut-points for fructosamine or glycated albumin have been small (N<200) and the study populations have typically not been well characterized [1, 2]. Furthermore, the literature on glycated albumin has largely focused on persons in Japan, Korea, and other Asian populations, where the assay is in wider clinical use [3-7].

We will define a healthy population within the ARIC study to establish reference intervals for 1,5-AG, fructosamine and GA overall and in demographic subgroups. We will also identify fructosamine and glycated albumin cut-points corresponding to values of HbA1c used for diagnosis and screening of diabetes (i.e., 5.7%, 6.5%). The information gained from this study will inform the clinical use of the Glycomark 1,5-AG and Roche fructosamine assays, which are already FDA cleared for clinical use in the US, and the Lucia GA-L glycated albumin assay, which is being submitted to FDA for approval.

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: Participants without diagnosed diabetes, obesity, or a history of cardiovascular disease at ARIC Visit 2 (1990-1992). Sensitivity analyses will be conducted after sequential exclusion of other "non healthy" persons who are overweight or have hypertension, dyslipidemia (elevated total- or LDL-cholesterol, high triglycerides, low HDL), reduced kidney function, fasting glucose >=100 mg/dL, or HbA1c >=5.7%.

Laboratory Measurements: Measurements of fructosamine, glycated albumin, and 1,5-anhydroglucitol were conducted in 2012-2013 in serum samples originally obtained from participants at Visit 2 and stored since then at –80°C. The three assays were implemented on the Roche Modular P800 analyzer at the University of Minnesota.

1,5-anhydroglucitol (1,5-AG) was measured in serum using GlycoMark 1,5-AG reagent on a Roche Modular P800 Chemistry Analyzer (Roche Diagnostics Corporation). First the sample is pretreated by glucokinase (GK) to convert glucose to glucose 6-phosphate in the presence of adenosine triphosphate (ATP), pyruvate kinase (PK) and phosphoenol pyruvate (PEP). The purpose of this reaction is to alter glucose so it cannot react in the

primary assay for 1,5-AG. Then pyranose oxidase oxidizes the second hydroxyl of 1,5-anhydroglucitol. The amount of hydrogen peroxide generated in this reaction is directly related to serum 1,5-AG concentrations and is detected by colorimetry using peroxidase. The lower and upper limits of detection are: (0.0 µg/mL, 330.0 µg/mL). CVs were 3.8% at a mean concentration of 4.63 µg/mL and 1.28% at a mean concentration of 14.67 µg/mL.

Fructosamine was measured in serum on the Roche Modular P800 Chemistry Analyzer (Roche Diagnostics Corporation) using a colorimetric assay based on the ability of ketoamines to reduce nitrotetrazolium-blue (NBT) to formazan in an alkaline solution. The rate of formation of formazan is directly proportional to the concentration of fructosamine. Uricase serves to eliminate uric acid interference and detergent eliminates matrix effects. The rate of reaction is measured photometrically at 546 nm. The lower and upper limits of detection are: (10 µmol/L, 2000 µmol/L). CVs were 3.2% at a concentration of 212.6 umol/L and 2.5% at a concentration of 856.7 umol/L%.

Glycated Albumin (and albumin) were measured in serum. This is a complex method by Asahi Kasei Pharma adapted to the Roche Modular P800 Chemistry Analyzer (Roche Diagnostics Corporation). The assay requires separate measurements of total albumin (bromcresol purple) and glycated albumin (enzymatic method utilizing ketoamine oxidase and an albumin-specific protease) measured in serum or plasma. The glycated albumin result is expressed as a percentage of total albumin (Formula: [(glycated albumin concentration in g/dL / serum albumin concentration in g/dL)*100/1.14] + 2.9). For albumin, the lower and upper limits of detection are: (1 g/dL, 16 g/dL). For glycated albumin, the lower and upper limits of detection are: (1 g/dL, 12 g/dL). For albumin: CVs were 1.9% at a concentration of 4.48 g/dL and 4.0% at a concentration of 2.5 g/dL. For glycated albumin: CVs were 2.3% at a concentration of 1.579 g/dL and 2.8% at a concentration of 0.426 g/dL.

Statistical analyses: We will examine distributions and summary statistics (mean, SD, min, max, median, p25, p50, p75, p95, p99) of each biomarker in the overall healthy subgroup before and after exclusions and in groups stratified by age, sex, and race. We will visually display and compare the distributions before and after exclusions and across subgroups using histograms and forest plots. We will examine correlations with HbA1c and fasting glucose and evaluate percentiles of each biomarker corresponding to clinical cut-points for HbA1c (5.7 and 6.5%) and fasting glucose (100 and 126 mg/dL).

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)?

ARIC Manuscript Proposal #2114 - Prognostic utility of fructosamine and glycated albumin for incident diabetes and microvascular complications Elizabeth Selvin

ARIC Manuscript Proposal #2113 - The associations of fructosamine and glycated albumin with vascular outcomes Elizabeth Selvin

ARIC Manuscript Proposal #2429 - Short-term variability of markers of hyperglycemia Christina Parrinello

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.

References

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