

The ARIC Publications Committee
Drs. Coresh, Sharrett, Szklo

December 12, 2016

Dear Dr. Sharrett and the ARIC Publications Committee:

My co-authors and I would like to submit for EXPEDITED ARIC review our addendum to our proposal “Comparative genetics of fructosamine, glycated albumin, and 1,5-anhydroglucitol in the Atherosclerosis Risk in Communities Study” (ARIC MS #2387) and the resulting manuscript “Genome-wide association study of 1,5-anhydroglucitol identifies genetic loci linked to glucose metabolism”. In addition to the analyses outlined in the manuscript that is currently under ARIC review, we are now submitting an addendum to also include an analysis of exome chip genetic data in the manuscript. The scientific rationale can be found in the accompanying addendum.

Because it is only an addendum of an existing paper that adds another level of genotypes to the same scientific question as well as due to the time-sensitive nature of the manuscript, we would like to request **ARIC limited review** for this addendum and very much appreciate the quick turn-around times of one week.

Please do not hesitate to contact me if there are any questions.

Sincerely,

Anna Kottgen

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ARIC Manuscript Proposal #2387

PC Reviewed: 7/8/14
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Comparative genetics of fructosamine, glycated albumin, and 1,5-anhydroglucitol in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):

Glycemic markers genetics

2. Writing Group:

Writing group members:

Nisa M. Maruthur, MD, MHS

Mandy Li, MHS

Anna Kottgen, MD, MPH

Kari North, PhD

Hao Mei, MD, PhD

Alanna Morrison, PhD

James Pankow, PhD

Eric Boerwinkle, PhD

Elizabeth Selvin, PhD, MPH

WH Linda Kao, PhD, MHS

Other suggestions welcomed

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

May-June 2014: Analyses

July-August 2014: Draft manuscript

September-October 2014: Revise manuscript and submit for ARIC review

4. Rationale:

Hemoglobin A1c (HbA1c) is used for the diagnosis of diabetes and is the major clinical test for adequacy of glycemic control (1). A given HbA1c value estimates average blood glucose over two to three months and correlates more strongly with average glucose than a single fasting glucose (2). However, HbA1c values may differ between individuals because of biologic factors unrelated to blood glucose such as red blood cell turnover and the affinity of hemoglobin for glucose (3). For example, HbA1c is less accurate in the setting of certain conditions (e.g., anemia, sickle cell disease) and the use of certain medications (4). Furthermore, a subset of single nucleotide polymorphisms (SNPs) predictive of HbA1c (e.g., rs4737009 (*ATP11A*) and rs7998202 (*ANK1*)) do not associate with blood glucose (5), and these genetic variants are likely non-glycemic determinants of HbA1c.

Glycated albumin, fructosamine, and 1,5-anhydroglucitol (1,5-AG) are alternative glycemic markers measured in serum or plasma; they reflect circulating glucose over shorter periods of time (1-2 weeks) as compared to HbA1c. Fructosamine and glycated albumin assays measure glycated proteins circulating in the serum, instead of glycated hemoglobin from red blood cells; based on the turnover of serum proteins, they estimate average glucose over 2-4 weeks. Serum levels of 1,5-AG reflect the amount of glucose excreted in the urine and thus decreases proportionally to glucose at and above the glomerular filtration threshold for glucose (180 mg/dl); this measure provides information on hyperglycemia over one week.

The limitations of HbA1c have been hotly debated – in particular the possibility that racial differences in HbA1c are unrelated to glucose (3). In this context, additional glycemic markers such as glycated albumin, fructosamine, and 1,5-AG could offer an alternative to HbA1c when the accuracy of HbA1c is questioned. Recently results from the ARIC Study demonstrated that the predictive and prognostic value of fructosamine and glycated hemoglobin were similar to HbA1c for the development of diabetes and its complications (6), and 1,5-AG appeared to add predictive information on long-term microvascular complications in addition to HbA1c in persons with diabetes (cite Selvin – under review). Fructosamine and glycated albumin levels were also found to be higher (6) and 1,5-AG levels lower (cite Selvin – under review) in African Americans vs. whites in ARIC.

5. Main Hypothesis/Study Questions:

Given the significant associations between these “newer” glycemic markers and diabetes and its complications and the debate around the clinical utility of HbA1c in persons of African ancestry, we propose to evaluate the genetic determinants of fructosamine, glycated albumin, and 1,5-AG through:

1) Evaluation of the contribution of global ancestry in blacks to these alternative glycemic markers

2) Genome-wide association studies in blacks and whites separately

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: Analysis of global ancestry and genome-wide association study

Inclusion: Participants with data on variables of interest and consenting to genetic and non-cardiovascular disease research

Exclusions: Participants with diabetes at visit 1 or 2; fasting glucose ≥ 180 mg/dl (for 1,5-AG analyses only)

Dependent variables: Serum fructosamine, glycated albumin, and 1,5-AG (visit 2)

Independent variable for global ancestry analysis: percentage of European ancestry (for global ancestry)

Covariates for global ancestry analysis: age, sex, center, BMI, physical activity, smoking alcohol, hypertension, CHD, serum albumin, eGFR, fasting glucose, fasting LDL, fasting HDL, fasting triglycerides (visit 2); education, income (visit 1)

Independent variables for GWAS: imputed genotypes (1000G) from GWAS (and possible exome chip and exome sequence data for follow up); principal components

Data analysis:

Sample size available:

	Fructosamine	Glycated albumin	1,5-AG
Whites	7,655	7,655	7,607
Blacks	2,117	2,117	2,076

Global ancestry (in blacks only): Evaluation of association between natural log transformed percentage of European ancestry and glycemic markers (fructosamine, glycated albumin, and 1,5-AG) using multivariate linear regression. Evaluation of net reclassification (7) associated with ancestry.

GWAS: We will perform linear regression to test for the association between genetic variants and ln levels of each glycemic marker (fructosamine, glycated albumin, and 1,5-

AG) stratified by black and white race, assuming an additive genetic model with a threshold of significance of 5×10^{-8} . We will follow standard ARIC quality control procedures for GWAS and adjust for principal components of ancestry. Findings from each population (black or white) will be specifically examined in the other population for potential replication. We will interrogate loci using a 250 kb window or recombination hotspots flanking the index SNP. Significance of replicated loci will be determined by the number of loci that are looked up. Replication with CARDIA, Framingham, and/or DCCT/EDIC will be considered if results in whites are not replicated in blacks.

Limitations: The main limitation of this analysis is limited sample size for the GWAS. Replication in other populations of the same ancestry may not be possible.

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)?

#2114 – "Prognostic utility of fructosamine and glycated albumin for incident diabetes and microvascular complications"

#2113 – "The associations of fructosamine and glycated albumin with vascular outcomes"

#2112 – "The prognostic value of 1,4-anhydroglucitol"

ARIC Manuscript Proposal #2387 – ADDENDUM

PC Reviewed: 12/13/16
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Comparative genetics of fructosamine, glycated albumin, and 1,5-anhydroglucitol in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):

Glycemic markers genetics

2. Writing Group:

Same writing group as for approved proposal #2387.

Note that the first author has changed over the course of the project from Nisa Maruthur to Mandy Li (1,5-AG related project) and to Stephanie Loomis (fructosamine, and glycated albumin related project).

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

First author: Mandy Li

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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:

Analyses will occur immediately.

4. Rationale:

As outlined in the original ARIC MS proposal #2387, genome-wide association studies of non-traditional glycemc markers have the potential to provide novel insights into mechanisms underlying hyperglycemia and diabetes. The already approved ARIC project therefore proposed to carry out these genetic analyses using genotyped and imputed genome-wide SNP data.

5. Main Hypothesis/Study Questions:

We already have completed all approved analyses and drafted a manuscript “Genome-wide association study of 1,5-anhydroglucitol identifies genetic loci linked to glucose metabolism”. In the final phase prior to manuscript submission we are trying to address one limitation of the current manuscript: replication data could not be obtained for some genome-wide significant novel findings because few cohorts have 1,5-AG measured. We therefore propose to investigate the exome chip genetic data within ARIC, which may a) allow us to assess that novel findings for imputed SNPs are valid using genotyped data (if available); b) increase the available sample size for African American participants thus allowing a targeted investigation of novel findings among European ancestry participants among the African Americans, and c) to carry out exome-chip wide association analyses for 1,5-AG for both EA and AA participants. Any novel finding from the latter approach would be focus of a separate manuscript, however.

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 has not changed from the initially approved MS #2387, other than that exome chip genotypes will be used as exposure instead of imputed genome-wide SNP array data.

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)?

#2387 - Comparative genetics of fructosamine, glycated albumin, and 1,5-anhydroglucitol in the Atherosclerosis Risk in Communities Study

#2114 – "Prognostic utility of fructosamine and glycated albumin for incident diabetes and microvascular complications"

#2113 – "The associations of fructosamine and glycated albumin with vascular outcomes"

#2112 – "The prognostic value of 1,5-anhydroglucitol"

#1309 – "Genome-wide admixture mapping analyses of cardiovascular and related metabolic traits"

- 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 (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/anic/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/anic/index.php>, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.