1.a. Full Title: Non-traditional glycemic markers and the risk of abdominal aortic aneurysm in persons with and without diabetes mellitus: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Novel glycemic markers & AAA

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

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3. Timeline: Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next year.

4. Rationale:
   Abdominal aortic aneurysm (AAA) is an asymptomatic but fatal disease with mortality rate of 75% to 90% when itruptures,1 and thus its prevention is critical. Major risk factors for AAA include older age, male sex, smoking, hyperlipidemia, and hypertension, which overlap with those for other cardiovascular diseases such as coronary heart disease and stroke.1,2,3 In this
context, it is intriguing that several studies have shown that diabetes mellitus, one of the strongest risk factors for cardiovascular diseases, is actually related to a lower risk of AAA.\textsuperscript{4,5,6}

A few potential mechanisms behind this paradoxical observation have been suggested. For example, hyperglycemia might increase collagen synthesis,\textsuperscript{7} and slow down the matrix loss, which is necessary for the pathogenesis of AAA.\textsuperscript{8} which may decelerate the matrix loss that are necessary for the pathogenesis of AAA. Moreover, the glycation of matrix might promote the formation of advanced glycation end products, which might increase smooth muscle cell proliferation and crosslinks between elastin and collagen in the vessel wall and stiffens the wall.\textsuperscript{5}

These potential mechanisms due to hyperglycemia are in line with a few studies showing that fasting glucose and hemoglobin A1c (HbA1c) are inversely related to AAA risk among both diabetic and non-diabetic persons.\textsuperscript{9,10} One the other hand, a few recent studies indicated that some antidiabetic medications like metformin may play a role in delaying AAA progression in diabetes, possibly by reducing aortic inflammation, elastin degradation and smooth muscle cell depletion.\textsuperscript{11,12,13,14}

In this context, the ARIC Study provides us a unique opportunity to explore the prospective associations of a few non-traditional glycemic markers (glycated albumin, fructosamine, 1,5-anhydroglucitol [1,5-AG]) with incident AAA as well as abdominal aortic diameter in persons with and without diagnosed diabetes over time. These non-traditional glycemic markers have some unique properties beyond traditional glycemic markers (i.e., fasting glucose and HbA1c). Specifically, those non-traditional glycemic markers reflect average glycemia over 2-3 weeks whereas HbA1c represents glycemia over 2-3 months. Additionally, 1,5-AG is considered to reflect postprandial glycemic excursions.\textsuperscript{15} By comprehensively quantifying the associations between different glycemic markers and AAA, we could better understand the contributions of hyperglycemia to the development of AAA. Also, longitudinal data of diabetes diagnosis and use of antidiabetic medications in ARIC will allow us to update these variables over time and extensively explore their interactions with non-traditional and traditional glycemic markers at baseline or their main effects regarding AAA risk. We will also cross-sectionally evaluate the associations of non-traditional and traditional glycemic markers with ultrasound-based abdominal aortic diameter at visit 5 (2011-13).

5. **Main Hypothesis/Study Questions:**

1) Fructosamine and glycated albumin will be inversely associated with AAA risk independently of potential confounders in both participants with and without diagnosed diabetes. 1,5-AG will be positively associated with AAA risk independently of potential confounders in participants with diabetes.

2) Fructosamine and glycated albumin will be inversely, and 1,5-AG will be positively associated with abdominal aortic diameter independently of potential confounders in both participants with and without diagnosed diabetes.

3) The associations with glycemic markers will be stronger in participants taking antidiabetic medications compared to whom do not.

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:
Hypotheses 1) and 3) will be tested using prospective study design, with visit 2 as baseline (visit 4 data as sensitivity analysis).

Hypothesis 2) and 3) will be tested using cross-sectional study design for visit 5.

Inclusions:
- All black and white ARIC subjects with data on glycemic markers (see below for details) at visit of interest and data on AAA during follow-up or abdominal aortic diameter at visit 5.

Exclusions:
- Ethnicity other than black or white
- Missing data on diabetes measurements or AAA outcome
- Prevalent AAA cases at visit 2 for primary prospective analysis (prevalent cases at visit 4 for secondary prospective analysis)
- Not fasting for 8h

Variables: Availability of key variables across visits and annual follow-up (AFU) are summarized in a table on the next page.

Exposures (independent variables):
- Glycemic markers: Visit 2 will be our primary baseline for the prospective analysis, but we will rerun analyses using visit 4 as baseline as a sensitivity analysis (excluding AAA patients diagnosed before visit 4).
  - Non-traditional: glycated albumin, fructosamine, and 1,5-AG
  - Traditional: fasting glucose and HbA1c.

Key potential effect modifiers:
- Diabetes mellitus: defined as a self-reported physician diagnosis of diabetes, or on treatment for diabetes in the past 2 weeks.
- Antidiabetic medications: Given the availability in annual follow-up, a comprehensive variable of taking antidiabetic medications or not would be our primary variable. However, for some analyses, when the situation allows, we will try to explore some of the following medications individually: metformin, sulfonylureas, thiazolidinedione (TZD), alpha-glucosidase inhibitors, meglitinide, dipeptidyl peptidase-4 inhibitors and sodium-dependent glucose transporters 2 inhibitors (SGLT 2 inhibitors) (using available medications at visit 2 or 4).

Outcomes (according to MP #2367):
- Clinical AAAs will be ascertained based on the following ICD diagnostic or procedure codes on discharge record or death certificates from visit 1 until the latest event data available at the time of analysis: 441.3 (abdominal aneurysm, ruptured), 441.4 (abdominal aneurysm without mention of rupture), 38.44 (resection of vessel with replacement, aorta, abdominal) and 39.71 (endovascular implantation of other graft in abdominal aorta), I71.3 (abdominal aortic aneurysm, ruptured), and I71.4 (abdominal aortic aneurysm, without rupture). These diagnoses would include both symptomatic and asymptomatic AAAs that were medically documented. The CMS data will be used to
identify additional hospital and outpatient AAAs. Identification of outpatient AAAs from the CMS data requires two claims that were at least seven days apart.

- **Visit 5 abdominal aortic diameter:** We will model proximal, mid, and distal aortic diameter separately as continuous outcome variables. We will also treat as a dichotomous outcome variable by using a wide cutoff of diameter $\geq 30$ mm.$^{16}$

**Other variables of interest and covariates:**
- Socio-demographics: age, race, gender, education
- Medical history: history of peripheral artery disease, CHD and stroke
- Physical examination: blood pressure, height, body mass index (or waist circumference), HDL and LDL cholesterol, eGFR
- Lifestyle: smoking status (current, former, never) and pack-years of smoking, alcohol habit
- Comorbidities: dyslipidemia, hypertension
- Antihypertensive medication and cholesterol-lowering medication

**Availability of variables:**

<table>
<thead>
<tr>
<th>Glycemic markers</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>AFU</th>
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</thead>
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<tr>
<td>Glycated albumin</td>
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<tr>
<td>1,5-AG</td>
<td>✓</td>
<td></td>
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</tr>
</tbody>
</table>

**Effect modifiers**
- Diabetes Mellitus diagnosis: ✓ ✓ ✓ ✓ ✓ ✓ ✓
- Simple antidiabetic meds (yes/no): ✓ ✓ ✓ ✓ ✓ ✓ ✓
- Individual antidiabetic meds: ✓ ✓ ✓ ✓ ✓ ✓ ✓

**AAA related**
- Clinical AAAs: Hospital diagnoses and death certificates
- Abdominal aortic diameter: ✓

**Statistical analysis plan:**

For the prospective analysis, we would fit Cox proportional hazards regression models to examine the prospective association of glycemic markers with incident AAA. Non-traditional and traditional glycemic markers from visit 2 will be individually modeled as continuous and categorical variables. We will stratify by diabetes status (diagnosed vs. undiagnosed as well as on diabetic treatment vs. not on diabetic treatment). We will also examine the interaction by diabetes status by modeling its product terms with a glycemic marker of interest. Since glycemic markers and medication use are likely to change across visits, we will also run the analyses using time-varying variables, whenever available. The aforementioned covariates would be adjusted for these analyses.
For the cross-sectional analysis, we will run linear regression models with aortic diameter as an outcome variable and glycemic markers as independent variables. We will also run logistic regression models for prevalent AAA based on ultrasound ≥30 mm.

We would conduct several sensitivity analyses. Firstly, we will conduct subgroup analysis stratified by sex, age, race, smoking, hypertension status, and a history of cardiovascular disease. Significance of interaction would be tested using likelihood ratio test. We are particularly interested in a potential interaction of glycemic markers and smoking, since a few studies demonstrated that smoking is not strongly associated with the progression of peripheral artery disease in diabetes\textsuperscript{17,18,19} but smoking is one of the strongest risk factor for AAA.\textsuperscript{1} Secondly, we would exclude participants with a history of cardiovascular disease at baseline to reduce the probability of including subclinical AAA cases into analyses.\textsuperscript{8} Thirdly, we will further account for competing risk.

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)?

MP2916 “Diabetes-related factors and abdominal aortic aneurysm risk: the Atherosclerosis Risk in Communities Study” is most relevant. However, this proposal was focusing on fasting glucose, insulin, and leptin but not HbA1c or non-traditional glycemic markers. Also, ultrasound-based abdominal aortic diameter was not covered in this previous proposal. Most importantly, the author group of MP2916 already published an original article in Annals of Epidemiology 28 (2018) 102-106.
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* AS 2009.18: “Identifying Genetic and Epidemiological Risk Factors for Abdominal Aortic Aneurysm”, R01HL103695, PI: Weihong Tang )

   ___ 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.cscenc.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.cscenc.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


