ARIC Manuscript Proposal # 2941

PC Reviewed: 02/14/20147   **Status:** _____   **Priority: 2**
SC Reviewed: _____   **Status:** _____   **Priority:** ____

1.a. Full Title:
Cross-sectional and prospective comparisons of 1,5-anhydrogluicitol and the oral glucose tolerance test

1.b. Abbreviated Title (Length 26 characters):

1,5-AG and OGTT

2.   Writing Group: Bethany Warren; Alexandra K. Lee; Ron Hoogeveen; Christie Ballantyne; James S. Pankow; Anna Köttgen; Elizabeth Selvin; others welcome

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

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3.   Timeline:

We intend to complete this proposal within a year of approval, as the data necessary for these analyses are currently available.

4. Rationale:

Current clinical guidelines recommend the use of fasting glucose, glycated hemoglobin (HbA1c), or the oral glucose tolerance test for diagnosis of diabetes.[1] Of the three traditionally used measures, the oral glucose tolerance test (OGTT) has long been viewed as the "gold standard" for diabetes diagnosis, although it has fallen out of favor in clinical practice, largely due to its inconvenience. The OGTT is burdensome for both the patient and the healthcare system, as it requires at least a 10-hour fast, ingestion of 75-g of glucose, and timed blood draws over two hours. In addition to these challenges, it also has well-documented high within-person variability.[2] Nonetheless, the OGTT was the long-standing basis for diabetes diagnosis and has been shown to be associated with a number of outcomes, including retinopathy, cardiovascular mortality, and all-cause mortality.[3–5]

1,5-anhydroglucitol (1,5-AG) is an emerging biomarker of hyperglycemia that could serve a similar purpose as OGTT. 1,5-AG is a 6-carbon monosaccharide that competes for reabsorption with glucose in the renal tubules and is thus excreted in the urine when glucose levels exceed the renal threshold, causing plasma 1,5-AG concentrations to drop. Consequently, low plasma 1,5-AG reflects periods of hyperglycemia. Specifically, 1,5-AG is highly correlated with glucose excursions (i.e., plasma glucose values greater than ~140-160 mg/dL) occurring over the prior ~2 weeks.[6] In prior studies, 1,5-AG has been shown to be associated with incident diabetes, retinopathy, chronic kidney disease, cardiovascular disease, and all-cause mortality, particularly among those with diagnosed diabetes.[7,8] Unlike OGTT, 1,5-AG does not require patient preparation or a carbohydrate challenge, however data directly comparing 1,5-AG to OGTT are sparse.

Given that both 1,5-AG and OGTT are measures of glycemic excursions, it is reasonable to posit that 1,5-AG may identify cases of undiagnosed diabetes defined by the OGTT, and may be similarly associated with incident diabetes and future diabetes-related microvascular and macrovascular complications. To our knowledge, however, no previous study has compared 1,5-AG and OGTT in the setting of a large epidemiologic cohort. The concurrent measurement of OGTT and 1,5-AG at visit 4 and the over two decades of follow-up of ARIC participants for multiple complications presents the opportunity to formally compare these biomarkers not only for the identification of persons with prevalent diabetes in the community but also for their prognostic value with respect to major clinical complications.

5. Main Hypothesis/Study Questions:

The overall goal of these analyses is two-fold:

Aim 1: To cross-sectionally determine whether 1,5-AG identifies cases of undiagnosed diabetes defined by OGTT (or fasting glucose) in the community.

Aim 2: To compare the prospective associations and prognostic value of 1,5-anhdyroglucitol and OGTT (and fasting glucose) for future diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality.

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 /Exclusions

Aim 1: We will conduct a cross-sectional analysis at Visit 4 (1996-98). Participants will be excluded from the analyses if they had prevalent diabetes (i.e., self-report of a physician diagnosis of diabetes or self-report of medications for diabetes) or chronic kidney disease at baseline, are missing glucose or 1,5-AG measurements, information on covariates, or did not fast for 10 or more hours.

Aim 2: We will conduct a prospective analysis, with Visit 4 (1996-98) as baseline. In addition to the exclusions outlined for Aim 1, participants will also be excluded if they have prevalent cardiovascular disease or stroke at baseline.

Variables

Aim 1: We will assess 1,5-AG continuously in comparison to OGTT and fasting glucose to identify persons with undiagnosed diabetes. We will compare 1,5-AG to OGTT 2-hour glucose $\geq$ 200 mg/dL and fasting glucose $\geq$126 mg/dL. Potential cutpoints for 1,5-AG will be identified by the methods described below:

Category	Definitions
ROC curve	• We will generate cutpoints using the Youden's Index
Percentiles	• We will calculate the percentile identified by OGTT and FG cutpoints and apply the same threshold for 1,5-AG (on the lower end of the distribution)
Previous retinopathy results/values from literature	• We will consider those with 1,5-AG $\leq$ 10 µg/mL to have diabetes by this definition[7]

Aim 2: We will compare the associations of 1,5-AG, OGTT, and fasting glucose with long-term clinical outcomes. Several outcomes will be assessed prospectively, per the definitions below:

Category	Definition
Incident diabetes	• Self-report of a physician diagnosis of diabetes or use of anti-diabetic medication at an ARIC visit or during an annual follow-up telephone call through 2015
Chronic Kidney Disease	• An estimated glomerular filtration rate-creatinine (eGFR-Cr) < 60 mL/min/1.73 m^2 at a subsequent study visit and an eGFR-Cr decline from baseline visit of at least 25%; or • Hospitalization or death related to chronic kidney disease; or • An end stage renal disease event identified by the United States Renal Data System registry
Cardiovascular disease	• Adjudicated coronary heart disease hospitalization events or death • Adjudicated ischemic stroke hospitalization events or death
All-cause mortality	• Ascertained from hospital and National Death Index records

Model 1 will be unadjusted.

Model 2 covariates will be measured at baseline and will be limited to age, sex, and race-center. Model 3 covariates will include Model 2 covariates + body mass index, total cholesterol, HDL, triglycerides, eGFR, hypertension, smoking status, drinking status, and family history of diabetes.

Statistical Analyses

Aim 1: We will generate scatterplots overall and by age, sex, and race between 1,5-AG and OGTT and fasting glucose to assess their relationships. We will construct ROC curves of 1,5-AG vs. OGTT and 1,5-AG vs. fasting glucose to evaluate concordance and identify potential cutpoints using the various methods described previously. We will assess the sensitivity and specificity of 1,5-AG for detecting OGTT- and fasting glucose-defined diabetes.

We will then assess whether the 1,5-AG definitions identify individuals with different risk factor profiles than those identified by OGTT or fasting glucose. Means, standard deviations and frequencies will be compared stratified by the various categorical definitions. Baseline characteristics that will be considered include age, sex, race-center, body mass index, percent obese, waist-to-hip ratio, education level, fasting glucose, 1-5, AG, 2-hour glucose, hypertension, hypercholesterolemia, smoking status, drinking status, eGFR, and family history of diabetes.

Aim 2: We will use Cox models with restricted cubic splines to flexibly model the association of each biomarker with the different outcomes. We anticipate, in particular, the relationship of 1,5-AG with outcomes to be non-linear. We will generate both unadjusted and adjusted models (Model 1, Model 2, and Model 3).

We will calculate Harrell's c-statistic to compare risk discrimination of the models. We will compare a base model comprised of age, sex, and race-center (Model 2), to models that add each biomarker separately to the base model, and to models that add combinations of the biomarkers to the base model. In particular, we are interested in whether 1,5-AG provides more prognostic value than OGTT, and whether 1,5-AG provides additional information to FG in this setting more than OGTT and/or beyond OGTT. We will also calculate the continuous Net Reclassification Index to quantify whether there is any improvement in classification using 1,5-AG as opposed to OGTT or fasting glucose.

Limitations

HbA_{1C} is not available at Visit 4. We will conduct sensitivity analyses comparing 1,5-AG to HbA_{1C} from Visit 2 to help address this limitation.

7.a. Will the data be used for non-CVD analysis in this manuscript?

    ___ Yes   _X_ No

7.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

__ 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)?**

#2112
#1588

**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/

**12.a. 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.**

12.b. 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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3. De Vegt, F. *et al.* Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: The Hoorn study. *Diabetologia* **42,** 926–931 (1999).

4. The DECODE Study Group on behalf of the European Diabetes Epidemiology Group. Glucose Tolerance and Cardiovascular Mortality. *Arch. Intern. Med.* **161,** 397–405 (2001).

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7. Selvin, E. *et al.* Association of 1,5-anhydroglucitol with diabetes and microvascular conditions. *Clin. Chem.* **60,** 1409–1418 (2014).

8. Selvin, E. *et al.* Association of 1,5-Anhydroglucitol With Cardiovascular Disease and Mortality. *Diabetes* **65,** 201–8 (2016).