

ARIC Manuscript Proposal #3483

PC Reviewed: 10/8/19
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Is serum 1,5 anhydroglucitol a sensitive biomarker indicating the use of sodium glucose transporter 2 inhibitors? The ARIC study

b. Abbreviated Title (Length 26 characters): 1,5 AG and SGLT2 inhibitors

2. Writing Group: Mahesh Mathew
Writing group members: Mahesh Mathew
Jim Pankow
Elizabeth Selvin
Anna Köttgen
Jung-Im Shin
Morgan Grams

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

First author: Mahesh Mathew

Address:

2900 4th St. SE
APT # 446C
Minneapolis- 55414
Minnesota, United States

Phone: 507-206-8839

Fax:

E-mail: mathe635@umn.edu

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).

Name: Jim Pankow, PhD, MPH

Address: Division of Epidemiology and Community Health
University of Minnesota
1300 S. 2nd St., Suite 300
Minneapolis, MN 55454

Phone: 612-624-2883

Fax:

E-mail: panko001@umn.edu

3. Timeline: Begin analysis October 2019; completed draft May 2020

4. Rationale:

1,5 anhydroglucitol (1,5 AG) competes with glucose for reabsorption in the renal tubules and is a marker of short term glycemic control^{1,2,3,4,5,6}. Glycosuria interferes with reabsorption of 1,5 AG and is associated with lower serum 1,5 AG levels (<10 µg/ml). The association was found to be stronger with the severity of the glycosuria: serum 1,5 AG levels were often ≤ 2 µg/ml in severe and persistent glycosuria^{2,7}. 1,5 AG level, which can be assessed through the commercial GlycoMark test,⁸ is a marker of glycosuria associated with hyperglycemic excursions in the prior 1-2 weeks^{2,7}. It is a more rapid indicator for recent changes in glycemic control [~ 2 weeks (1,5 AG) vs 8–10 weeks (HbA1c)]⁷.

Consistent with its role as an indicator of glycemic control, serum 1,5-AG increases when patients with type 2 diabetes mellitus (T2DM) are treated with diabetes medications such as metformin, glimepiride, or pioglitazone⁹. By contrast, SGLT2 inhibitors, a relatively new class of anti-diabetic medications, act by competitively inhibiting the reabsorption of glucose in the renal tubules¹⁰ and are associated with lower rather than higher serum levels of 1,5 AG^{2,7}. This reduction in 1,5 AG levels, despite more favorable changes in other glycemic markers, is due to the competitive inhibition of 1,5 AG reabsorption by the glucose excreted in urine secondary to the SGLT2 inhibitor action⁷.

In a recent study⁷, 1,5 AG measurements were available in a convenience sample of 292 diabetic patients who had been prescribed SGLT2 inhibitors. Among 240 patients taking SGLT2 inhibitors at the time of their 1,5 AG measurements, the average 1,5 AG levels was 1.2 µg/ml and 92% of patients had levels ≤ 2 µg/ml. The average 1,5 AG levels in 52 patients not taking the SGLT2 inhibitors was 6.4 µg/ml and only 12% had values ≤ 2 µg/ml. In another study², 1,5 AG levels decreased by an average of 5.7 µg/ml over 26 weeks in 20 diabetic patients randomized to an SGLT2 inhibitor (canagliflozin) and increased by an average of 1.0 µg/ml in 20 diabetic patients randomized to placebo.

Although there are reports of lower levels of 1,5 AG in diabetic patients taking SGLT2 inhibitors, use of low 1,5 AG as a marker SGLT2 inhibitor use has not been studied in great detail. This manuscript will investigate the association of SGLT2 inhibitor use with levels of 1,5 AG and other glycemic markers in members of the ARIC cohort.

5. Main Hypothesis/Study Questions:

Compared to users of other diabetes medications, users of SGLT2 inhibitors have lower serum levels of 1,5 AG despite similar levels of other glycemic markers (fasting glucose; hemoglobin A1c).

The inverse association between 1,5 AG and other glycemic markers will be stronger in users of other diabetes medications compared to users of SGLT2 inhibitors.

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).

Design: This will be a cross-sectional analysis of data collected at visit 6. Analysis will be repeated using data from visit 7 when available.

Primary variables of interest: 1,5 AG, fasting glucose, hemoglobin A1c, diabetes diagnosis, medication classes derived from the medication inventory.

Other variables of interest: age, sex, race/center

Data analysis: Recognizing that confounding by indication is a serious threat to validity when assessing medication effects in observational data, analysis will be restricted to individuals taking diabetes medications in order to focus on individuals with diagnosed, treated diabetes. The primary analysis will use linear regression, with 1,5 AG level as the dependent variable and SGLT2

inhibitor use (yes/no) as the main predictor. Covariates will include age, sex, and race/center. To assess whether differences in 1,5 AG level by SGLT2 inhibitor use persist after controlling for long-term hyperglycemia, models will additionally adjust for HbA1c and fasting glucose. Sensitivity analyses will explore the effect of additional adjustment for other types of diabetes medication, or number of diabetes medications. To assess whether the inverse association between 1,5 AG and HbA1c is different in users of other diabetes medications compared to users of SGLT2 inhibitors, we will add an interaction term (HbA1c*SGLT2 inhibitor) to the above models. To study the effect of dose of SGLT2 on 1,5 AG, an exploratory analysis will be carried out (depending on the number of SGLT2 takers). We will also explore adding an indicator for the presence of loss of function alleles in *SLC5A10*, the main 1,5 AG transporter, as these gene variants have been shown to have large effects on 1,5 AG levels¹¹.

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/mantrack/maintain/search/dtSearch.html>

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)?

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 (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 <https://www2.csc.unc.edu/aric/approved-ancillary-studies>

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/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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