PC Reviewed: 4/9/13	**Status: <u>A</u>**	**Priority: <u>2</u>**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The prognostic value of 1,5-anhydroglucitol

  b. Abbreviated Title (Length 26 characters): Prognostic value of 1,5-AG

2.   Writing Group:
     Writing group members: Elizabeth Selvin; Andreea Rawlings; James S. Pankow; Frederick L Brancati; Michael Steffes; Josef Coresh; others welcome

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

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3.   Timeline: We aim to submit this paper for ARIC review <1 year from approval of the manuscript proposal

4.   Rationale:

1,5-anhydroglucitol (1,5-AG) reflects hyperglycemic excursions and is thought to be a useful indicator of short-term (1-2 week) hyperglycemia. 1,5-AG is a monosaccharide, originating mainly from foods and closely resembling glucose in structure. It is not readily metabolized and is typically present at high but constant concentrations in the

blood. 1,5-AG is freely filtered by the glomeruli and, under normal circumstances, is completely reabsorbed in the renal tubule. However, urinary excretion is accelerated in the setting of hyperglycemia—high concentrations of glucose block re-absorption of 1,5-AG in the kidney—so excess circulating glucose levels will cause serum 1,5-AG concentrations to fall. In the setting of hyperglycemia, serum 1,5-AG concentrations are thought to serve as a measure of short-term glycemia. A commercial assay for 1,5-AG (GlycoMark[TM]) is marketed in the U.S. (approved by FDA in 2003), is available at major U.S. laboratories, and is reimbursed by Medicare.

The attractiveness of 1,5-AG is that it may capture additional information on glycemic excursions that are not reflected in HbA1c, fructosamine, or glycated albumin (1). A growing literature provides evidence that 1,5-AG may provide a useful complement to HbA1c measurements (1-7). Previous studies suggest that post-prandial glycemic excursions may be an independent risk factor for cardiovascular disease (8-12) although this contention is controversial (13-15). To the extent that hyperglycemic post-prandial excursions are important in atherogenesis, 1,5-AG may provide independent information regarding cardiovascular risk (9). Nonetheless, few studies have compared 1,5-AG to other markers of glycemia in a population-based setting. Our aim is to assess the utility of 1,5-AG in identifying individuals at high risk for cardiovascular disease, diabetes, and kidney disease alone and in combination with other glycemic markers.

5.   Main Hypothesis/Study Questions:
The overarching objective of this study is to characterize the associations of 1,5-AG with cardiovascular disease, diabetes, and chronic kidney disease in the community-based ARIC Study. Because 1,5-AG concentrations are substantially lowered only when circulating glucose concentrations are very high, we hypothesize that an association of 1,5-AG with clinical outcomes may only be observed at very low concentrations of 1,5-AG. In a small pilot study, we have previously shown that low concentrations of 1,5-AG are associated with diabetes risk but only at very low concentrations, suggesting a threshold effect (6). Because 1,5-AG is filtered by the kidney, we will pay particular attention to the associations with prevalent and incident chronic kidney disease and how kidney disease may mediate any associations of 1,5-AG with cardiovascular risk.

Hypotheses:

Hypothesis 1: 1,5-AG will be inversely associated with the risk of cardiovascular outcomes and kidney disease among persons with and without a history of diabetes before and after adjustment for potential confounding factors.

Hypothesis 2: 1,5-AG will add independent prognostic information to HbA1c and fasting glucose as a marker of cardiovascular risk in persons with and without diabetes.

Hypothesis 3: Very low concentrations of 1,5-AG will be associated with incident diabetes among persons with no history of diagnosed diabetes at baseline.

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: Prospective cohort analysis with visit 2 (1990-1992) as baseline

Exposures: 1,5-AG measured in 2012-2013 at the University of Minnesota as part of Dr. Selvin's ancillary study from stored serum samples originally collected at visit 2 (1990-1992).

Exposures (for comparison): HbA1c and fasting glucose

Outcomes: The focus of this study will be the associations of 1,5-AG with cardiovascular events, total mortality, incident and prevalent kidney disease, and incident diabetes (visit-based and post-visit 4 self-reported cases among persons without a history of diabetes at baseline). We anticipate that any association of 1,5-AG with all-cause mortality will be driven primarily by fatal cardiovascular events.

Coronary heart disease: We will define incident coronary heart disease cases using the composite definition incorporating definite or probable myocardial infarction, cardiac procedures, and deaths from coronary heart disease identified during the follow-up visits (silent myocardial infarctions) and during active surveillance for all hospitalizations and deaths among ARIC participants.

Ischemic stroke: We define incident stroke as an adjudicated (definite or probable) incident ischemic stroke event identified during active surveillance.

Mortality: Death from any cause identified during active surveillance of all participants in the ARIC study.

Incident diabetes: we will use two definitions of diabetes, a visit-based definition and an interview-based definition. Visit based diabetes will be defined based on serum glucose measurements, a self-reported diagnosis of diabetes, or medication use at the subsequent three ARIC visits (maximum of 6 years of follow-up) (16). Interview-based diabetes will be defined on the basis of a self-reported diabetes diagnosis or diabetes medication use during the ARIC visits and subsequent annual follow-up telephone calls.

Prevalent chronic kidney disease: cases of prevalent chronic kidney disease will be defined as those persons with glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 estimated from serum creatinine measured at baseline (visit 2).

Incident chronic kidney disease: We will use established definitions of incident chronic kidney disease as previously defined in the ARIC Study (17). Specifically, we will define incident chronic kidney disease as a glomerular filtration rate (GFR)

<60 ml/min/1.73 m^2 estimated from serum creatinine measured at visit 4 (1996 – 1998), visit 5 (2011-2013), or a kidney disease hospitalization or death identified by continuous active surveillance of all hospitalizations. End-stage renal disease (ESRD) is comprised of the subset of hospitalizations indicating kidney transplant or dialysis (18). We will conduct sensitivity analyses to compare definitions based on estimated glomerular filtration rate, a creatinine rise, a hospitalization for kidney disease, or combinations of the aforementioned events.

Exclusions: Missing information on exposures or covariates of interest, a history of cardiovascular disease at or before baseline (visit 2), race other than white or black, and blacks in the Minneapolis and Washington County cohorts. Persons who are non-fasting will be excluded from comparative analyses of fasting glucose. Persons with prevalent chronic kidney disease will be excluded from analyses of incident kidney disease. Persons with prevalent diabetes will be excluded from analyses of incident diabetes.

Stratification: We will conduct analyses overall and stratified by history of diagnosed diabetes based on self-reported physician diagnosis or diabetes medication use at or before visit 2. We anticipate that any observed associations with clinical outcomes may primarily be present among those persons with high glucose levels (undiagnosed diabetes and diagnosed diabetes). We will examine the association of 1,5-AG with clinical outcomes across clinical (diabetes diagnostic) categories of HbA1c at baseline to understand whether 1,5-AG may contribute further risk information within baseline HbA1c groups.

Statistical analyses: We will estimate hazard ratios and their 95% confidence intervals using Cox proportional hazards models. We will consider the following core models:

    Model 1: age, sex, race-center.
    Model 2: age, sex, race-center, low-density and high-density cholesterol concentrations, triglyceride concentration, body mass index, waist-to-hip ratio, systolic blood pressure, hypertension medication use, family history of diabetes, education level (visit 1), alcohol use, physical activity (visit 1), and smoking status.
    Model 3: all variables in Model 2 + HbA1c (per %-point)
    Model 4: all variables in Model 2 + fasting glucose (per mg/dL)
    Model 5: all variables in Model 2 + estimated GFR (ml/min/1.73 m^2)

We will model 1,5-AG in diabetes-specific quartiles and also continuously. To characterize the continuous associations, we will generate piece-wise linear splines with knots corresponding to the cutoffs for the quartiles and we will also implement restricted cubic splines to obtain a smoother fit to the data. Model discrimination will be assessed using Harrell's C statistic. We will test for interactions by race and prevalent chronic kidney disease at baseline. To evaluate the overall improvement in risk classification for the addition of 1,5-AG to the fully adjusted model including HbA1c, we will calculate the net-reclassification improvement statistic (NRI) and the integrated-discrimination improvement statistic (IDI) (19).

Testing for thresholds: In our spline models, we will compare the slopes of the splines to evaluate possible changes in slope in the piece-wise linear model. To more formally test for the presence of thresholds (change points) we will maximize the likelihood ratio with respect to the location of the threshold in each model and use bootstrap methods to derive the p-value for the presence of a threshold across the range of the parameter (20).

Sensitivity analyses: We will conduct sensitivity analyses to evaluate the potential effect of including/excluding persons with chronic kidney disease at baseline in the analyses of incident cardiovascular disease and diabetes. Using linear regression models, we will explore the association of 1,5-AG with baseline kidney function (defined by estimated GFR) to understand whether adjustment for eGFR may be important in the prospective analyses.

Limitations:
- Reliance on a single measurement of 1,5-AG
- Because the vast majority of the ARIC baseline population is non-diabetic, we will have a low prevalence of hyperglycemia, which may limit the prognostic performance of 1,5-AG, which is thought to be most relevant in the hyperglycemic range. Nonetheless, we have shown in a previous pilot study of a subsample of the ARIC population that 1,5-AG is associated with prevalent microvascular conditions and incident diabetes.
- The prevalence of reduced kidney function in the ARIC population is low, thus we may have limited power to fully explore the possible effects of reduced kidney function (and especially very reduced kidney function) on 1,5-AG and its potential mediating effect on long-term risk.
- As with all observational studies, we will not be able to eliminate the possibility of residual confounding despite rigorous adjustment for known risk factors.

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)?

Associations of alternative markers of glycemia with hemoglobin A(1c) and fasting glucose. Juraschek SP, Steffes MW, Selvin E. Clin Chem. 2012 Dec;58(12):1648-55. doi: 10.1373/clinchem.2012.188367. Epub 2012 Sep 27. PMID: 23019309

Alternative markers of hyperglycemia and risk of diabetes. Juraschek SP, Steffes MW, Miller ER 3rd, Selvin E. Diabetes Care. 2012 Nov;35(11):2265-70. doi: 10.2337/dc12-0787. Epub 2012 Aug 8. PMID: 22875225

Racial differences in glycemic markers: a cross-sectional analysis of community-based data. Selvin E, Steffes MW, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL. Ann Intern Med. 2011 Mar 1;154(5):303-9. PMID: 21357907

Nontraditional markers of glycemia: associations with microvascular conditions. Selvin E, Francis LM, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL, Steffes MW. Diabetes Care. 2011 Apr;34(4):960-7. doi: 10.2337/dc10-1945. Epub 2011 Feb 18. PMID: 21335368

Glycated hemoglobin and the risk of kidney disease and retinopathy in adults with and without diabetes. Selvin E, Ning Y, Steffes MW, Bash LD, Klein R, Wong TY, Astor BC, Sharrett AR, Brancati FL, Coresh J. Diabetes. 2011 Jan;60(1):298-305. doi: 10.2337/db10-1198. Epub 2010 Oct 26. PMID: 20978092

Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. N Engl J Med. 2010 Mar 4;362(9):800-11. doi: 10.1056/NEJMoa0908359. PMID: 20200384

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.

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