ARIC Manuscript Proposal #2590

PC Reviewed: 8/11/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Association of 1,5-Anhydroglucitol with subclinical cardiovascular disease

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
Writing group members: Menglu Liang; John William (Bill) McEvoy; Yuan Chen; Michael Steffes; A. Richey Sharrett; Elizabeth Selvin

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]**

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3. Timeline:

Analysis is to start as soon as approval is obtained. We anticipate completion of the manuscript within one year from approval of the proposal.

4. Rationale:

1,5-Anhydroglucitol (1,5-AG) is a dietary monosaccharide and resembles glucose structurally[1 2] . Given that 1,5-AG competes with glucose for reabsorption in the renal tubules, plasma 1,5-AG is a glucose analog that shows extremely stable concentrations when its intake and excretion are balanced. However, in the setting of hyperglycemia, high amounts of glucose block tubular reabsorption of 1,5-AG, causing serum concentrations to fall. Thus, 1,5-AG is thought to be a useful indicator of postprandial glucose excursions and short-term (1–2 week) hyperglycemia [3 4].

Hyperglycemia and diabetes are well-known risk factors for cardiovascular disease[5 6 7]. Also, a growing body of evidence shows that postprandial hyperglycemia and glycemic variability are independent risk factors for cardiovascular complications in persons with diabetes[8 9 10]. A previous investigation in the ARIC study demonstrated an association between 1,5-AG and incident cardiovascular events[11]. However, the association of 1,5-AG with subclinical cardiovascular disease is relatively uncharacterized.

Cardiac troponin is a highly specific marker of acute myocardial infarction [12]. Given its high sensitivity and specificity as well as strong correlation with irreversible myocardial cell damage[13], troponin has been extensively used to identify myocardial cell necrosis even without symptoms of chest pain and electrocardiographic changes [14 15]. New high-sensitivity cardiac troponin T (hs-cTnT) assays can detect troponin concentrations far below the conventional limit of detection of standard assays and have recently been applied to asymptomatic populations. Recent studies have demonstrated the prognostic value of these hs-cTnT assays for independently predicting future cardiovascular events[16 17] including in the ARIC Study[18 19]. Indeed, there is growing evidence that hs-cTnT is a useful marker of chronic subclinical myocardial damage[12] .

Carotid intima–media thickness (CIMT) is a well-established surrogate of atherosclerosis and has been shown to be associated with prevalent and incident cardiovascular disease (CVD)[20 21]. Evidence has shown elevated fasting glucose concentration is associated with increased CIMT level, while it is still unclear whether elevated fasting glucose causes increased level of CIMT[22]. Also we have shown glucose excursions are independently in contributing to endothelial dysfunction and vascular damage[11]. In this context, 1,5-AG as a hyperglycemic excursion may help to further understanding the observed association.

The ARIC Study has rigorous measurements of 1,5-AG, hs-cTnT, and CIMT all obtained at the same visit (visit 2, 1990-1992). Thus, the objective of this study will be to evaluate the cross-sectional associations of 1,5-AG with hs-cTnT and CIMT, two important and potent measures of subclinical cardiovascular disease. We will conduct a secondary analysis examining the association of 1,5-AG with incident elevated hs-cTnT (>=14 ng/L) among persons who had a second hs-cTnT measurement obtained at visit 4 (1996-1998), 6-years after first measurement at visit 2 (1990-1992).

5. Main Hypothesis/Study Questions:

Hypothesis: 1,5-AG will be cross-sectionally associated with both subclinical myocardial damage (assess by hs-cTnT) and subclinical atherosclerosis (assessed by CIMT), particularly in persons with diabetes. A second aim will be to evaluate the

prospective association of 1,5-AG with incident subclinical myocardial damage among persons with measurements of hs-cTnT obtained at two time points, 6 years apart.

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: Cross-sectional analysis using visit 2 (1990-1992) data. Secondary prospective analysis looking at incident elevated hs-cTnT at visit 4 (1996-1998).

Study Population:

The Atherosclerosis Risk in communities (ARIC) Study is a community-based prospective cohort study which enrolled over 15,792 participants from four US communities (Forsyth Country, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland). Details of the study design are previously published[23]. The first clinic examinations (visit 1) took place from 1987 to 1989, with 3 follow-up visits approximately every 3 years. The fifth visit was completed in 2011– 2013. The second clinic examination (visit 2) took place from 1990 to 1992 and is the first visit for which measurements of 1,5-AG are available in all participants and will be used as the baseline for the present study. There were 14,348 participants who attended visit 2 in total. Institutional review boards at each site reviewed and approved the study protocols and informed consent was obtained from all participants.

Inclusion/exclusion criteria:

Main Analyses

Inclusion criteria: Participants who attended visit 2 and had valid measurements of key exposures, covariates, and outcomes

Exclusion criteria:

1) Race other than white or black; non-whites in Minnesota and Washington County
2) Persons with a history of clinical cardiovascular disease at or prior to visit 2
3) Fasting less than 8 hours
4) Missing data on any key exposures, covariates, or outcomes

Secondary Analyses

Additional Exclusion criteria:

1) Participants who had a hs-TnT concentration over 14 ng/L at visit 2

2) Missing data on hs-TnT at visit 4

Definitions of Diabetes Mellitus:

Diabetes mellitus will be defined as a self-reported physician diagnosis of diabetes mellitus, current use of glucose-lowering medications, a fasting glucose value ≥126mg/dL or a hemoglobin A1c (HbA1c) value ≥6.5%.

Exposure:

Measurement of 1,5-AG

1,5-AG was measured in 2012–2013 in stored serum samples obtained from participants visit 2 (1990–1992) using materials from GlycoMark, Inc on a Roche Modular P800 system (Roche Diagnostics Corp., Indianapolis, IN). Details of the GlycoMark assay have been described before [24].

Outcomes:

Measurement of hs-cTnT

Cardiac troponin T was measured at visit 2 (1990-1992) and visit 4 (1996-1998), using the same highly sensitive sandwich immunoassay method (Roche Elecsys T, Roche diagnostics, Indianapolis, IN). Hs-cTnT was measured in stored serum samples collected at visit 2 using a Roche Elecsys 2010 Analyzer (Roche Diagnostics) at the University of Minnesota in 2012-2013. Hs-cTnT was also measured in stored plasma samples collected at visit 4 using a Cobas c411 analyzer (Roche Diagnostics) at Baylor College of Medicine. A standard calibration study was conducted to evaluate the reliability of hs-cTnT across specimen type and laboratory. No significant differences were detected and no statistical correction was indicated [25].

Measurement of carotid intima-media thickness

To assess carotid IMT, B-mode carotid ultrasound (Biosound 2000 II SA; Biosound, Indianapolis, IN) evaluations were completed on bilateral segments of the extracranial carotid arteries in all participants who attended the ARIC visit 2 examinations. Mean far wall thickness was calculated as the mean of six far wall sites 1 cm long taken from the right and left carotid bifurcation, common and internal carotid arteries. If the participants had missing IMT information from any carotid artery site, values were imputed for missing sites based on sex and race. Mean far wall CIMT was also adjusted for reader differences and measurement drift over the visit[26]. The 6-site mean imputed value will be used in analysis.

Other variables

All covariates used in the regression models were measured at visit 2 except education, race, and sex, which were assessed at visit 1. Serum glucose was measured using the hexokinase method. HbA1c was measured in stored whole blood samples using high-performance liquid chromatography with instruments standardized to the Diabetes Control and Complications Trial assay (Tosoh A1c 2.2 and Tosoh G7)[27]. Plasma lipid concentrations[28 29 30 31], body mass index[32], and blood pressure [33] were also measured. Hypertension will be defined as the mean of the second and third readings at the visit (with cutoff for systolic blood pressure of 140 mmHg or higher and/or a cutoff for diastolic blood pressure of 90 mmHg or higher) or the use of hypertension medication. Participants reported their alcohol use and smoking status.

Statistical analyses

Consistent with our prior ARIC papers on this topic, 1,5-AG level will be divided into five categories according to diabetes mellitus status and 1,5-AG concentration. Persons with diabetes will be divided into 3 groups based on 1,5-AG concentrations (<6, 6 to <10, and ≥10 ug/mL), and persons without diabetes will be divided into 2 groups according to concentrations of <10 and ≥ 10 ug/mL. Participants without diabetes and 1,5-AG concentrations ≥ 10 ug/mL will be used as the reference group. Cross sectional analyses will be performed using multivariable regression models. Elevated hs-TnT will be defined as a concentration of ≥ 14 ng/L at visit 2. For elevated hs-TnT, logistic regression models will be used to estimate the adjusted odds ratio (ORs) and their corresponding 95% CIs. For average mean level of carotid IMT, linear regression models will be used to estimate the adjusted coefficients and their corresponding 95% CIs. For thick CIMT(the determination of the top cIMT quartile and also top decile), logistic regression models will be used to estimate the adjusted odds ratio (ORs). We will conduct a secondary analysis among those who had valid measurements of hs-TnT while not in elevated group at visit 2 to estimate the prospective association between baseline 1,5-AG at visit 2 and incident elevated hs-TnT at visit 4. For incident elevated hs-TnT, Poisson regression models will be used to estimate the adjusted relative risk (RR) and their corresponding 95% CIs. In the sensitive analyses, we will conduct multinomial regression models to account for CVD and non-CVD deaths for the incident elevated hs-TnT. To characterize the associations of 1,5-AG with incident elevated hs-TnT outcome, Cox proportional hazards models will be used to estimate hazard ratios and their corresponding 95% confidence intervals and proportional hazard assumption will be tested. To characterize the continuous association of 1,5-AG and incident elevated hs-TnT, linear and restricted cubic spline will be fit with four knots placed at 3, 6, 10, 14 ng/L and hazard ratio (HR) equals to one will be the reference group. We will compare two models for each outcome. Model 1 will be adjusted for age, gender and race-center (white participants, Minnesota, Maryland, Mississippi, and North Carolina; black participants, North Carolina). Model 2 will be adjusted for all variables in model 1 plus plasma lipid concentrations (LDL cholesterol, HDL cholesterol and triglycerides), systolic blood pressure, blood pressure lowering medication use, lipid lowering medication use, current alcohol status, current smoking status, Estimated Glomerular Filtration Rate (eGFR), C-reactive protein and body mass index. To characterize the possible independent prognostic value for 1,5-AG, we will also conduct sensitivity analyses using self-report diagnosis of diabetes as the definition for diabetes mellitus and estimate the associations in Model 1, Model 2, Model 3 (variables in model 2 plus HBA1C) and Model 4 (variables in model 2 plus fasting glucose).

For the prospective analyses of incident elevated hs-cTnT, we will use methods to formally address missing data at visit 4. Considering the missing data due to attrition and death between visits 2 and 4, we will employ an inverse probability of attrition weighting (IPAW) approach to account for missing data. Persons with diabetes and high values of hs-cardiac troponin may be more likely to die or withdraw from the study, which might cause bias on the estimation of association between 1,5-AG and incident elevated hs-TnT. We will develop separate logistic regression models to account for dropout due to death and attrition. Also additional models will be used to predict death and attrition and then the probability gain from the additional models will be multiplied by the weights

calculated from the original logistic models to get the standardized inverse probability weights. Results from Poisson regression models, multinomial regression models and IPAW will be compared to address the prognostic value of 1,5-AG at visit 2 for incident elevated hs-TnT at visit 4.

Limitations

We will not be able to establish temporality in the cross-sectional analyses. We only have only a single measurement of 1,5-AG at baseline. Also because of the observational setting, we can not rule out the possibility of residual confounding even after adjusting for rigorously measured risk factors for cardiovascular disease.

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
_____ 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
__X__ A. primarily the result of an ancillary study (list number* 2009.16)
__X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2013.25)

*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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

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