ARIC Manuscript Proposal #2607

PC Reviewed: 9/8/15 Status: A Priority: 2
SC Reviewed: _________ Status: _____ Priority: ____

1.a. Full Title: 1,5-Anhydroglucitol and cognitive function in older adults

   b. Abbreviated Title (Length 26 characters): 1,5-AG, cognition v5

2. Writing Group:
   Writing group members: Andreea M. Rawlings, A Richey Sharrett; Thomas Mosley; Michael W Steffes; Alden Gross; Josef Coresh; Elizabeth Selvin, others welcome

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

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3. Timeline: All data is currently available, we plan to submit for publication within 6 months of approval of the manuscript proposal.
4. Rationale:
A growing body of evidence has found that diabetes affects performance in several cognitive domains, is associated with greater cognitive decline, and puts persons at increased risk of dementia\(^1\)–\(^5\). However the pathophysiologic mechanisms by which diabetes leads to cognitive dysfunction are not well understood. A number of mechanisms have been proposed as possible contributing factors, including increased formation of advanced glycation end products, insulin resistance, oxidative stress, and episodes of hypo- and hyperglycemia,\(^6\)–\(^9\).

Fluctuations in glycemia have also been shown to adversely affect endothelial function and may lead to the development of vascular complications\(^10\),\(^11\), and a few studies have examined the association between hyperglycemic excursions and cognitive function. In a randomized trial of older adults where participants were randomized to either repaglinide or glibenclamide, both groups experienced significant, and similar, declines in hemoglobin A1c and fasting plasma glucose, however the group randomized to repaglinide also showed a significant decline in the coefficient of variation of postprandial plasma glucose (measured using 2-hour postprandial glucose). This group showed no decline in cognitive function over 12 months compared to the glibenclamide group, which experienced significant cognitive decline over the same period\(^12\).

Additionally, a few cross-sectional studies using continuous glucose monitors (CGMs) have found associations between cognitive function, glycemic variability, and mean amplitude of glycemic excursions (MAGE)\(^13\)–\(^15\).

1,5-anhydroglucitol (1,5-AG) is a monosaccharide, similar to glucose in structure. In the presence of hyperglycemic episodes (levels above the renal threshold, approximately 180 mg/dL), 1,5-AG competes with glucose for renal re-absorption, causing serum levels to fall. As a result, 1,5-AG reflects hyperglycemic excursions over a short period of time (1-2 weeks), and research with CGMs has found strong correlations between excursions and serum levels of 1,5-AG\(^16\). In contrast, HbA1c is a measure of average glycemic levels, whether they vary widely or not.

Our aim is to test the hypothesis that 1,5-AG, a marker of hyperglycemic excursions, is associated with lower cognitive function, independent of HbA1c and other risk factors.

5. Main Study Questions:
To test the hypothesis that 1,5-AG, a marker of hyperglycemic excursions, is associated with lower cognitive function, independent of HbA1c and other risk factors.

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 study using data from visit 5 (2011-2013)
Exclusions
We will exclude participants who meet any of the following criteria:
- Do not have diagnosed diabetes, defined using self-reported diagnosis or medication use. We will also define diabetes using both HbA1c (≥6.5%) and fasting glucose (≥126 mg/dL)
- Race other than black or white, and blacks in Minneapolis or Washington County centers
- Missing cognitive tests at visit 5 (as a sensitivity analysis, we will impute global Z scores for these participants)
- Missing covariates included in statistical models (listed below)

Exposure
1,5-AG will be modeled continuously and categorically. We will use cut-points suggested by the manufacture (6 and 10 ug/mL) and used in previous studies\textsuperscript{17}. We will also look at these markers dichotomized at the median within each category of HbA1c, and will compare across categories of 1,5-AG and a normal value of HbA1c.

Outcomes
The outcomes for this study are the cognitive function tests, which were assessed in all participants at visits 5 using the following standardized tests:
- Delayed word recall test (DWRT)
- Digit symbol substitution test (DSST)
- Word fluency test (WFT)
- Logical memory, parts I and II (LM-I, LM-II)
- Trail making test, parts A and B (TMT-A, TMT-B)
- Boston naming (BN)
- Animal naming (AN)
- Digit Span backwards (DSB)
- Mini-mental state exam (MMSE)
- Clock time and pentagons (a subset of the MMSE)

We will examine these tests individually, and grouped by domains. For each test, we will calculate a Z score by subtracting the test mean and dividing by the standard deviation. To create the domains, we will average the Z scores of tests in each domain.

The domains are:
- Language: AN, BN, WFT
- Processing speed and executive function: TMT-A, TMT-B, DSST, DSB
- Memory: DWRT, LM-I, LM-II
- Visuospatial: Clock-time and pentagons (analyzed separately as a binary variable)

We will also create a global measure of cognitive function by average Z scores across all tests.

Statistical Analysis:
We will characterize our analytic population using means (standard deviations) or N (%) for all covariates. Covariates include age, race/center, body mass index, education, hypertension, hypertension medication use, apoE genotype, smoking, alcohol use, physical activity, and eGFR.

We will analyze the association between 1,5-AG level and cognitive score using regression analysis and the following statistical models:

- Model 1: Crude/unadjusted
- Model 2: Model 1 + age, sex, race/field center, education
- Model 3: Model 2 + physical activity, smoking, alcohol use, body mass index, apoE4, hypertension, hypertension medication use, eGFR
- Model 4: Model 3 + HbA1c

Effect Modification
We will examine possible effect modification by race, sex, diabetes duration, and depression status.

Sensitivity analyses
Propensity score analysis:
Persons with different categories of both traditional and non-traditional biomarkers, regardless of diabetes status, may differ substantially on a number of demographic, behavioral, and clinical characteristics (such as A1c). The lack of comparability between these groups may limit the ability to control for confounding using traditional methods. As an alternative, we will use a stratified, propensity score matching approach to account for confounding.

Challenges/Limitations
- Single measurement of the non-traditional markers and each cognitive test
- The cross-sectional design limits our ability to draw firm conclusions regarding temporality or causality of any observed associations
- We will not be able to rule out the possibility of residual confounding
- Participants who attended visit 5 are likely different from those who did not. This raises concerns

7.a. Will the data be used for non-CVD analysis in this manuscript? __x__ 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? __x__ Yes ___ No

(This file ICTDER03 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? __x__ 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”? __x__ 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.cscce.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)?

MSP #2112: The prognostic value of 1,5-anhydroglucitol (Selvin)
MSP#1418: Glycemic control (hemoglobin A1c), cognitive decline and dementia risk: The Atherosclerosis Risk in Communities (ARIC) Study (Selvin)
MSP#1067: Glycemia (haemoglobin A1c) and incident stroke: The ARIC Study (Selvin)
MSP #1973: Cardiovascular exposures, cognitive decline, and depression in whites and blacks (Al Hazzouri)
MSP#2160: Diabetes and cognitive change over 20 years: the Atherosclerosis Risk in Communities Study (Rawlings)
MSP #672: Changes in cognitive test scores in the ARIC cohort over a 6-year period (visit 2 to visit 4) and their correlation with vascular risk factors (Knopman)

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* 2008.06)
   ____   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.cscce.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. Accepted

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.cscce.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.
References


