ARIC Manuscript Proposal #2828

1.a. Full Title: Association of 1,5-anhydroglucitol with MRI measures of neurodegeneration and cerebrovascular disease

b. Abbreviated Title (Length 26 characters): 1,5-AG and brain imaging

2. Writing Group:
   Writing group members: Andreea M Rawlings; Rebecca F Gottesman; Clifford Jack; David Knopman; Thomas H Mosley; Andrea LC Schneider; A Richey Sharrett; 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 12 months of approval of the manuscript proposal.
4. Rationale:
It is well documented that diabetes is associated with cognitive function and incident dementia. The pathogenesis that underlies these association is unclear, although a number of pathways have been suggested, including factors related to the primary metabolic changes associated with diabetes, such as insulin resistance, hypoglycemia, or to its treatment or complications.

Hemoglobin A1c (HbA1c) is a standard clinical measure used for diagnosis and management of diabetes, and reflects mean blood glucose over the previous 2-3 months. Several studies have shown that the risk of cognitive impairment increases at higher levels of HbA1c, but few have investigated associations of cognitive impairment, including findings on brain imaging, with glycemic peaks and variability.

1,5-anhydroglucitol (1,5-AG) is a monosaccharide similar to glucose in structure. When blood concentrations of glucose exceed the renal threshold (~180 mg/dL), 1,5-AG competes with glucose for re-absorption in the renal tubules, resulting in urine excretion of 1,5-AG and lower serum levels. Low blood levels of 1,5-AG have been shown to reflect hyperglycemic peaks over the preceding 7-10 days. Glycemic excursions are common in adults with diabetes, even those with good glycemic control (HbA1c <7%).

Glucose peaks and variability may be particularly relevant for cognitive function. A study of neuronal cells in vitro found that compared to sustained high (~450 mg/dL) or low (~45 mg/dL) ambient glucose levels, recurrent fluctuations between high and low glucose concentrations were more detrimental to mitochondrial activity in the neuronal cells. Studies have also shown that fluctuating glucose levels adversely affect endothelial function and potentially lead to the development of vascular complications, although much debate exists in the literature. Several studies that employed continuous blood glucose monitors demonstrated associations between measures of glycemic variability and brain atrophy, independent of mean levels of glycemia and hypoglycemic episodes. Our prior work in ARIC has found robust associations between 1,5-AG and incident stroke over 20 years, and between 1,5-AG and 20-year cognitive decline and incident dementia (manuscript proposal #2606, paper under review).

Studies using magnetic resonance imaging (MRI) can help clarify the pathogenesis in the association between diabetes and cognitive impairments. To date, studies have documented associations of diabetes with both cerebral atrophy (both global and regional) and vascular pathology. However, few studies have examined the role glycemic peaks may play in the neurodegeneration and ischemic changes observable on MRI.

Our aim is to characterize the association between 1,5-AG and brain MRI, including brain volumes (total and regional), white matter hyperintensity volume, the presence of cortical and lacunar infarcts, and the presence of microhemorrhages.
5. Main Study Questions:

Aim 1
To examine the association between 1,5-AG and measures of neurodegeneration, including total and regional brain volumes.

Aim 2
To examine the association between 1,5-AG and measures of cerebrovascular disease including white matter hyperintensity volume, presence of cortical and lacunar infarcts, and the presence of microhemorrhages.

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 using data from visit 5

Exclusions
We will exclude participants who meet any of the following criteria:
- Did not undergo MRI at visit 5 (or MRI of poor quality)
- Race other than black or white, and blacks in Minneapolis or Washington County centers
- Have a history of clinical stroke, multiple sclerosis, surgery or radiation to the skull or brain, or brain tumor
- Missing covariates (described below)

Exposure – 1,5-AG within categories of diabetes/HbA1c
Our exposure variable of interest 1,5-AG will be examined continuously (linearly and using splines) and categorically (dichotomized at 10 µg/mL per manufacturer recommendation) overall and within four categories defined by self-reported diabetes, glucose lowering medication, and HbA1c as follows:
- No diabetes: No self-reported diabetes, no use of glucose lowering medication, and HbA1c <5.7%
- Prediabetes: No self-reported diabetes, no use of glucose lowering medication, and HbA1c 5.7%-6.4%
- Diabetes, HbA1c <7%: self-reported diagnosis or use of glucose lowering medication and HbA1c <7% OR no report of diagnosis or medication use and HbA1c 6.5%-7% (undiagnosed diabetes)
- Diabetes, HbA1c ≥7%: self-reported diagnosis or use of glucose lowering medication and HbA1c ≥7% OR no report of diagnosis or medication use and HbA1c ≥7% (undiagnosed diabetes)
Outcome – measures from MRI:
MRI data at visit 5 including:
- Volumes:
  o Total brain volume
  o Regional brain volumes (temporal, parietal, occipital, and frontal)
  o Hippocampal
  o Alzheimer’s signature region (inferior parietal, hippocampus, precuneus, and cuneus)
  o White matter hyperintensities (WMH)
- Infarcts and microbleeds:
  o Number and presence of cortical and lacunar infarcts
  o Number and presence of microbleeds

To allow comparisons across regions, volumes will be standardized to Z scores by subtracting the mean and dividing by the standard deviation for each volume (total and regional). Because of its skewed distribution, WMH volume will be first log transformed then standardized.

Covariates
We will evaluate the following variables as covariates: age, sex, race-center, body mass index, education, hypertension, hypertension medication use, apoE genotype, smoking, alcohol use, diabetes duration (for the two diabetes groups), and physical activity. We will show associations both adjusted and unadjusted for HbA1c (adjustment made within each of the four exposure groups). Intracranial volume will be used as a covariate in all analyses of brain volumes except for WMH.

Statistical Analysis:
We will characterize our analytic population using means/standard deviations or percent for all covariates. For analyses of volumes, we will use linear regression with adjustment for covariates described above. For analyses of infarcts and microbleeds, we will use logistic regression, but we will also consider negative binomial and Poisson regression where the proportion with infarcts/microbleeds exceeds 10%.

Effect Modification
We will examine possible effect modification by age, race, and sex.

Sensitivity analyses
We will consider the following sensitivity analyses:
- Persons who underwent MRI may be healthier than those who did not and compared to those who did not attend visit 5. We will consider the use of inverse probability weighting or other methods to account for selection bias (e.g. Heckman correction)
- Because of the potential to misclassify persons when using HbA1c to defined diabetes, we will also use fasting glucose to define the four-level exposure variable described in the exposure section above.
- Persons with low HbA1c (<4.5-5%) have been shown to be at higher risk for death. We will conduct analyses after removing this group of participants.

**Challenges/Limitations**
- Single measurement of 1,5-AG
- We may have limited power in some analyses
- Selection bias of who ends up with an MRI is of concern and may limit generalizability of our study
- We will not be able to rule out the possibility of residual confounding

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.cscn.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)?

   MP #1553: Associations between vascular risk factors and longitudinal changes in ventricular size: a 14-Year longitudinal study (Knopman)
   MP #1771: Cognitive, Vascular Risk Factors, and APOE Genotype Predictors of Hippocampal Volume (Knopman)
   MP #2112: The prognostic value of 1,5-anhydroglucitol (Selvin)
   MP #2288: Associations of brain imaging with cognitive change over 20 years (Knopman)
   MP #2315: Association of diabetes with brain magnetic resonance imaging (Schneider)
MP #2606: Biomarkers of hyperglycemia, 20-year cognitive decline, and dementia risk: the Atherosclerosis Risk in Communities Study (Rawlings)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  
   _x_ Yes  ____ No  
   ARIC NCS

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.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.
References


