ARIC Manuscript Proposal # 1758

1.a. Full Title: Chronic Hyperglycemia and Arterial Stiffness: the Atherosclerosis Risk in the Communities Study

  b. Abbreviated Title (Length 26 characters): Chronic Hyperglycemia and Arterial Stiffness

2.   Writing Group: Jonathan Rubin; Vijay Nambi; Lloyd E. Chambless; Michael W. Steffes; Josef Coresh; A. Richey Sharrett; Elizabeth Selvin

     Writing group members:

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

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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).

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3.   Timeline: Data for this proposal are already available. We expect to complete the manuscript within the next 6 months.

4. Rationale:

In the United States an estimated 5.4 million individuals have been diagnosed with diabetes and around 2.4 million are undiagnosed [1]. Heart disease death rates among adults with diabetes are 2 to 4 times higher than the rates for adults without diabetes [2]. Diabetes affects the vasculature by various mechanisms; "atherosis" is a term which has been used to refer to lipid deposition in the vasculature to form intimal plaques while sclerosis refers to "vessel stiffening" [3]. The relationship between hyperglycemia and atherosis has been examined, but limited studies have addressed the role of hyperglycemia in the pathophysiology of sclerotic vascular disease.

Earlier studies suggested that insulin stimulates the proliferation of smooth muscles cells [4] and that hyperglycemia causes non-enzymatic glycosylation of proteins and stiffening of the vasculature [5, 6]. Data from ARIC has also shown that insulin resistance and elevated fasting glucose are associated with indices of increased arterial stiffness [7].

In ARIC, Liao et al. demonstrated that increased arterial stiffness was associated with the development of hypertension independently of other traditional cardiovascular risk factors [8]. Also, in a recent meta-analysis increased arterial stiffness was also shown to be a strong predictor of future cardiovascular events and all-cause mortality [9].

The association between chronic hyperglycemia, as assessed by hemoglobin A1c (HbA1c), and arterial stiffness in diabetics and non-diabetics has not been previously studied. Thus, we sought to examine the relationship between HbA1c and measures of increased arterial stiffness in the ARIC cohort.

5. Main Hypothesis/Study Questions:

Hypothesis:
Higher HbA1c values will be associated with increased arterial stiffness after controlling for socio-demographic and cardiovascular risk factors.
   a) The association above will be present both in persons with and without a history of diabetes.
   b) The association will be seen both for an index that does and one that does not adjust for arterial dimensions (Ep and YEM, respectively, see below) suggesting that HbA1c level is associated with altered material in the arterial wall.

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 methodological limitations or challenges if present).

Study design: Cross-sectional analyses of participants at ARIC visit 2.

Exposure: Hemoglobin A$_{1c}$ (HbA$_{1c}$) (available at visit 2 only)
We measured HbA1c from stored whole blood specimens in ARIC as part of ARIC Ancillary Studies #2003.5 and #2006.15. HbA1c data are available on all participants at ARIC Visit 2.

Outcomes:
Both outcomes were measured in participants during the ultrasound exam (visit 2).

A) Peterson's Elastic Modulus (EP)
EP = (Pulse Pressure * Diastolic Arterial Diameter) / (Arterial Diameter Change)

B) Young's Elastic Modulus (YEM)
YEM = (EP * Diastolic Arterial Diameter) / (2 * Intima Media Thickness)

Inclusions
All black and white ARIC subjects with data on HbA1c at visit 2 who have ultrasound measurements available (n ≈ 9,500).

Exclusions:
Ethnicity other than black or white, blacks with center Washington or Minnesota, missing HbA1c at visit 2, non-fasting at visit 2, missing ultrasound measurements at visit 2, less than 2 EKG cycles, or missing covariates of interest.

Definition of History of Diabetes
Subjects will be classified as having a history of diabetes if they report a physician diagnosis of diabetes or medications use for diabetes at either Visit 1 or Visit 2.

Covariates
Other variables of interest will include age, sex, race, center, smoking status, height, weight, hypertensive medication use, education, heart rate, triglycerides, HDL and LDL cholesterol and kidney function (estimated GFR from serum creatinine). Additional analyses will adjust for systolic BP (during ultrasound measurement), since, even in arteries with unaltered stiffness, the stiffness indices are believed to change with higher BP levels.

Statistical Analysis
HbA1c will be modeled as: (1) a continuous variable; and (2) in clinical categories in persons without a history of diabetes (<5.7, 5.7-<6.5 and ≥6.5%) and in persons with a history of diabetes (<7, 7-<8, ≥8%).

EP and YEM with be modeled as: (1) a continuous variable; and (2) by quartiles.

We will use linear and logistic regression models to assess the association between HbA1c and EP and YEM at visit 2. For example, multivariable logistic regression models

will be used to estimate odds ratios and corresponding 95% CIs for the highest quartiles of EP or YEM, by categories of HbA1c.

Without a priori interaction hypotheses, we will formally test for interaction between HbA1c level and gender, race, prevalent hypertension at baseline and use of hypertension medication. If effect modification is present, we will conduct stratified analyses.

<u>Limitations</u>
Around 25% of the cohort is missing ultrasonic measurements at visit 2. Additionally, the pulse pressure was measured at the brachial artery while the ultrasound measurement was performed in the carotid artery. Finally, despite adjustment for known cardiovascular risk factors, residual confounding cannot be excluded.

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 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? ____ 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)?

Proposals on the association between carotid ultrasound and cardiovascular disease
MP#2 B-mode ultrasound: associations with CHD factors (A)
MP#3A Ultrasonic measurement of the elastic modulus of the common carotid artery: the ARIC study
MP#3B Variation of common carotid artery elasticity with intimal-medial thickness: The ARIC Study
MP#3C Hypertension and arterial stiffness: The Atherosclerosis Risk in Communities Study
MP#3E Non-insulin dependent diabetes mellitus, fasting glucose and insulin concentrations are associated with arterial stiffness indices: the ARIC Study
MP#6 Associations of lipoprotein cholesterols, apolipoproteins A-I and B, and triglycerides with carotid atherosclerosis and coronary heart disease: the Atherosclerosis Risk in Communities (ARIC)
MP#32 High resolution B-mode ultrasound scanning methods in the Atherosclerosis Risk in Communities Study (ARIC)
MP#33 High resolution B-mode ultrasound reading methods in the Atherosclerosis Risk in Communities (ARIC) Cohort
MP#34 Measurement of arterial distensibility in the Atherosclerosis Risk in Communities (ARIC) cohort
MP#77 Variability in ultrasonic measurements of arterial stiffness in the Atherosclerosis Risk in Communities Study
MP#78 Wall thickness and arterial distensibility: case-control approach (A)
MP#462 Carotid size and stiffness vs. incident events
MP#473 Carotid artery atherosclerosis and the risk of non-insulin dependent diabetes mellitus
MP#510 (D) Multiple metabolic syndrome (disorder) and arterial stiffness
MP#511 Arterial distensibility and physical activity in the ARIC study
MP#512 Arterial stiffness and the development of hypertension: the ARIC Study
MP#513 Association of arterial stiffness and cerebrovascular diseases
MP#514 Association of arterial stiffness and retinal microvascular
MP#515 Association af arterial stiffness and left ventricular hypertrophy
MP#516 Trait anger and arterial stiffness: results from the Atherosclerosis Risk in Communities study
MP#723 Arterial stiffness is greater in African Americans than in whites. Evidence from the Forsyth County, North Carolina ARIC Cohort
MP#1461 The association of arterial stiffness with incident cardiovascular disease

Proposals on the association between HbA1c and cardiovascular disease

MP#1024: Glycemic Control (HbA1c) and Coronary Heart Disease Risk in Persons with and Without Diabetes: The Atherosclerosis Risk in Communities Study
MP#1056r: Hemoglobin A1c (HbA1c) and Peripheral Arterial Disease in Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study
MP#1431 Hemoglobin A1c, glucose, and incident diabetes: the Atherosclerosis Risk in Communities Study

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __**X**__ **Yes** ____ **No**
ARIC Ancillary Study #2006.15, "Hemoglobin A1c (HbA1c), Incident Diabetes, and Major Causes of Morbidity and Mortality in Non-Diabetic Participants (HbA1cDM)."

11.b. If yes, is the proposal
   __**X**__   **A. primarily the result of an ancillary study (list number** __#2006.15__ **)**
   ____   **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/

12. 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.

References

1.	Selvin E, Coresh J and Brancati FL, The burden and treatment of diabetes in elderly individuals in the u.s. Diabetes Care, 2006. 29(11): p. 2415-9.
2.	Franco OH, Steyerberg EW, Hu FB, Mackenbach J and Nusselder W, Associations of diabetes mellitus with total life expectancy and life expectancy with and without cardiovascular disease. Arch Intern Med, 2007. 167(11): p. 1145-51.
3.	Blankenhorn DH and Kramsch DM, Reversal of atherosis and sclerosis. The two components of atherosclerosis. Circulation, 1989. 79(1): p. 1-7.
4.	Pfeifle B and Ditschuneit H, Effect of insulin on growth of cultured human arterial smooth muscle cells. Diabetologia, 1981. 20(2): p. 155-8.
5.	Brownlee M, Vlassara H and Cerami A, Nonenzymatic glycosylation and the pathogenesis of diabetic complications. Ann Intern Med, 1984. 101(4): p. 527-37.
6.	Lehmann ED, Gosling RG and Sonksen PH, Arterial wall compliance in diabetes. Diabet Med, 1992. 9(2): p. 114-9.
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8.	Liao D, Arnett DK, Tyroler HA, et al., Arterial stiffness and the development of hypertension. The ARIC study. Hypertension, 1999. 34(2): p. 201-6.
9.	Vlachopoulos C, Aznaouridis K and Stefanadis C, Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol, 2010. 55(13): p. 1318-27.