1. a. Full Title: Carotid Artery Calcification in Diabetes and the Influence of Renal Dysfunction

b. Abbreviated Title (Length 26 characters): Carotid Calcium in Diabetes.

2. Writing Group: Angela Muriithi, Bruce Wasserman, Brad Astor, Others welcome including Joe Coresh

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

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3. Timeline: Analyses to begin when proposal approved by committee. We hope to have our first draft of the manuscript prepared by June 1, 2007.

4. Rationale:
Vascular calcification has long been known to occur as a result of any vascular insult and inflammatory process. Various metabolic, inflammatory and mechanical mechanisms have been shown to promote ossification outside of the skeletal system. While the various mechanisms all result in ectopic calcification, they differ in their pathological characteristics and the disease conditions in which they are predominant. In addition, the location of calcium deposition within vessel wall is dependent on the initiating process.
itself. Diabetics typically develop calcification in the medial arterial wall, similar to that which occurs in chronic kidney disease⁴, as well as in the intimal wall, which occurs in atherosclerosis and perhaps in hypercholesterolemia⁵. The presence of arterial calcification is not merely a reflection of these pathologic processes but it is also a predictor of clinical outcome since it relates to an increase in morbidity and mortality⁵, particularly for diabetics⁶,⁷,⁸. This is in contrast to the stabilizing effect calcification has on the biomechanical properties of an individual plaque, as shown using computer models of in vitro coronary atheroma specimens⁹. The development of calcification may have an affect on the size of another important determinant of plaque vulnerability, the lipid core, since it forms within the core as soon as the core develops⁰.

The relationship between diabetes and arterial calcification has been shown in vivo using x-ray imaging such as in intramammary arteries by mammography¹¹, and in coronary arteries by computed tomography (CT)¹². CT has uncovered associations between coronary calcification and age, male gender and lipid profile¹³, and associations between atheromatous and medial calcification of the aorta and inflammation and C-reactive protein (CRP) production¹⁴,¹⁵. CT imaging of the carotid artery has been used to reveal clinical implications of calcium detection, such as its association with asymptomatic plaque and plaque inflammation¹⁶. These associations with vulnerable plaque have not been studied in diabetics. Moreover, carotid artery calcification has not been studied in diabetics. MRI has emerged as an alternative tool for detecting and quantifying vascular calcification. MRI can identify calcification without the need for the ionizing radiation of a CT exam, and mineral volumes measured by CT and MRI are highly correlated¹⁷.

We seek to determine the association of carotid artery calcification detected by MRI with diabetes in the participants of the ARIC Carotid MRI study and investigate the influence of renal dysfunction on this association. We will also investigate the effect of cardiovascular risk factors, such as cholesterol and CRP, on this relationship. We will further study the relationship between vascular calcification and vulnerable features of plaque such as the degree of enhancement and cap thickness, as well as the influence of diabetes and renal impairment on these associations.

5. Main Hypothesis/Study Questions:
1. The presence of diabetes will predict the presence of calcification in the carotid artery as it does in other vascular beds.
   a. The degree of calcification will be increased by the presence of renal insufficiency.
   b. The relationship above will be independent of other risk factors for arterial calcification (e.g., age, male gender and lipid profile).
2. We will explore the association of carotid artery calcification and other plaque characteristics measured by MRI (e.g., lipid core) in diabetics compared to those without diabetes.
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).

**Inclusion/Exclusion**
Selected internal carotid artery (SICA) images with QC scores of 1 or 2 will be studied. Those in whom the diagnosis for diabetes was not ascertained either by visit 4 of the ARIC study or at the clinical interview at the start of the Carotid MRI study will be excluded.

**Main Outcome**
The main outcome will be any measurement of calcium derived from the SICA. This will be used both as a dichotomous variable based on calcium presence, as well as a continuous variable based on total volume of calcium, maximum area of calcium at any slice and the area of calcium in the slice above the flow divider.

**Other MRI variables**
- Wall thickness (mean, max SICA at slice used for calcium area measurements)
- Lipid core size (total core volume, core area at slice with max calcium area)
- Fibrous cap thickness (minimum and mean cap thickness measurements at (a) the slice with the largest calcification area if lipid core present and (b) the slice with the largest lipid core)

**Dependent variables**
- Diabetes mellitus at ARIC MRI visit
- Cumulative diabetes variable over ARIC MRI visit and previous ARIC visit

**Covariates**
- Demographic data: age, sex, race
- Comorbid conditions: hypertension, obesity, etc.
- Medication use: lipid-lowering agents, phosphate binders, anti-hypertensives
- Anthropometric data: BMI, waist circumference, waist-hip ratio
- Social habits: smoking, alcohol intake, drug use
- Laboratory values will include hsCRP, IL-6, serum creatinine, lipids and lipoproteins (TC, LDL, HDL, Tg), urinary albumin

This will be based on data from the clinical visit of the MRI study, as well as from visit 4 of the ARIC study, when necessary.

The variables to be used to assess renal insufficiency will be based on National Kidney Foundation guidelines for defining chronic kidney disease: estimated glomerular filtration rate (eGFR), based on serum creatinine, and urinary albumin excretion.

**Analyses**
Descriptive statistics will be used to compare those with diabetes/glucose intolerance to those without. Univariate analysis of diabetes status and the presence of carotid calcification as a dichotomous and continuous variable will be done. The relationship between diabetes and carotid calcification, as modified by the presence of renal
dysfunction will also be investigated. We will explore the effect the other MR variables and covariates have on these relationships in multivariate analyses. Similar analyses will be performed using the “cumulative diabetes” variable.

A limitation of this study is that large areas of calcium are typically included within the lipid core area in the image analysis. We will attempt to correct for this by adjusting the lipid core area when a large area of calcium is identified in the same wall segment.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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.csec.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 1215 Association of Chronic Kidney Disease with carotid artery plaque characteristics

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

   b. If yes, is the proposal  
      _X__ A. primarily the result of an ancillary study (list number* 1997.02)
      ____ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

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**


