ARIC Manuscript Proposal #3026

PC Reviewed: 8/8/17 **Status:** _____ **Priority: 2**
SC Reviewed: _____ **Status:** _____ **Priority:** ____

1.a. Full Title: Galectin-3 and sonographic measures of carotid atherosclerosis.

  b. Abbreviated Title (Length 26 characters): **Galectin 3 and CIMT.**

2. Writing Group:
        Writing group members: Abayomi Oyenuga, Aaron Folsom, Oluwaseun Fashanu, David Aguilar, Christie Ballantyne.

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

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3. Timeline: Begin Summer 2017

4.   Rationale:

Inflammation plays a role in the progression of atherosclerosis.[1] In the last few decades, the scientific thinking about the pathogenesis of atherosclerosis has expanded to include other novel risk factors including chronic inflammatory markers or conditions of varying etiology[2] [3].

Examination of the carotid artery using ultrasound provides a means of evaluating alterations in the vessel wall structure that are predictive of future cardiovascular events.[4-6]. Carotid intima-media thickness (CIMT) and plaque/shadowing are indirect assessments of atherosclerotic burden, although the values obtained from these tests might not be representative of atherosclerosis elsewhere in the body [7-9]. Also, despite the varied etiology of atherosclerotic plaque development and the contribution of multiple factors to plaque evolution, CIMT appears to be reflective of vessel wall changes primarily due to aging and hypertension rather than a generalizable marker of the process of atherosclerosis [10, 11].

Macrophages are the main inflammatory cell type found in atherosclerotic plaques [12, 13], and galectin-3, a beta-galactoside binding lectin produced by these cells, has been shown to be an independent risk factor for coronary artery disease. [4] [Aguilar D et al. ARIC unpublished data]. Galectin-3 has been shown to play a valuable role in the regulation of immunological, inflammatory, and nutritional conditions[14] [15] some of which might be responsible for atherosclerotic plaque development and progression [16].

The aim of this study is to assess the association between serum galectin -3 levels and sonographic measures of carotid atherosclerosis in the ARIC study.

5.   Main Hypothesis/Study Questions:

1. Is serum galectin-3 correlated positively with measures of carotid atherosclerosis, namely, intima-media thickness and plaque/shadowing?
2. Does this association differ by age and/or sex?
3. Does the association differ depending on whether the common carotid, the bifurcation or the internal carotid intima-media thicknesses are considered?

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).

Design: Cross-sectional at Visit 4, with plasma galectin 3 concentration as the exposure.

Outcome: Carotid intima –media thickness (CIMT) measures (mm), plaque/shadowing (y,n) at Visit 4

Exclusions: Missing galectin-3, missing CIMT, missing plaque/shadowing measure, and missing co-variates.

Primary Covariates: Major atherosclerotic disease risk factors: age, sex, race (black, white), field center, total cholesterol, high-density lipoprotein cholesterol, use of lipid medication (yes, no), systolic blood pressure, antihypertensive medication use (yes, no), diabetes mellitus (yes, no), eGFR, smoking status, height, and weight.

Analysis: Examine association of galectin-3 with covariates. Test for normality of galectin-3 and CIMT distributions.

Main analysis – Linear regression – CIMT on galectin-3. Model 1 adjusted for demographics, Model 2 also adjusted for other risk factors and eGFR, and Model 3 also adjusted for CRP. Logistic regression - CIMT will be converted into a categorical variable using a cutoff of 0.9 mm, and similar models will be run.
The logistic regression analysis will also be done for the plaque/shadowing outcome.

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

   ___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)?

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

11.b. If yes, is the proposal
    ___ A. primarily the result of an ancillary study (list number* _____)
    ___ 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.

13. Per Data Use Agreement Addendum, approved manuscripts using 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 ____ No.

1. Libby, P., P.M. Ridker, and A. Maseri, *Inflammation and Atherosclerosis.* Circulation, 2002. **105**(9): p. 1135-1143.
2. Agca, R., et al., *Atherosclerotic cardiovascular disease in patients with chronic inflammatory joint disorders.* Heart, 2016. **102**(10): p. 790-795.
3. Sessa, R., et al., *Infectious burden and atherosclerosis: A clinical issue.* World J Clin Cases, 2014. **2**(7): p. 240-9.
4. Lisowska, A., et al., *Predictive value of Galectin-3 for the occurrence of coronary artery disease and prognosis after myocardial infarction and its association with carotid IMT values in these patients: A mid-term prospective cohort study.* Atherosclerosis, 2016. **246**: p. 309-17.
5. Nambi, V., et al., *Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study.* J Am Coll Cardiol, 2010. **55**(15): p. 1600-7.

6.   Bots, M.L., et al., *Carotid Intima-media Thickness Measurements: Relations with Atherosclerosis, Risk of Cardiovascular Disease and Application in Randomized Controlled Trials.* Chin Med J (Engl), 2016. **129**(2): p. 215-26.

7.   Kasliwal, R.R., et al., *Carotid intima–media thickness: Current evidence, practices, and Indian experience.* Indian J Endocrinol Metab, 2014. **18**(1): p. 13-22.

8.   Pasterkamp, G., et al., *Is plaque formation in the common carotid artery representative for plaque formation and luminal stenosis in other atherosclerotic peripheral arteries? A post mortem study.* Atherosclerosis, 1998. **137**(1): p. 205-10.

9.   Adams, M.R., et al., *Carotid intima-media thickness is only weakly correlated with the extent and severity of coronary artery disease.* Circulation, 1995. **92**(8): p. 2127-34.

10.   Qu, B. and T. Qu, *Causes of changes in carotid intima-media thickness: a literature review.* Cardiovasc Ultrasound, 2015. **13**.

11.   Mathiesen, E.B., et al., *Carotid Plaque Area and Intima-Media Thickness in Prediction of First-Ever Ischemic Stroke.* A 10-Year Follow-Up of 6584 Men and Women: The Tromsø Study, 2011. **42**(4): p. 972-978.

12.   Galkina, E. and K. Ley, *Immune and Inflammatory Mechanisms of Atherosclerosis.* Annu Rev Immunol, 2009. **27**: p. 165-97.

13.   Gerrity, R.G., et al., *Dietary induced atherogenesis in swine. Morphology of the intima in prelesion stages.* Am J Pathol, 1979. **95**(3): p. 775-92.

14.   Lu, Y., et al., *Modified citrus pectin inhibits galectin-3 function to reduce atherosclerotic lesions in apoE-deficient mice.* Mol Med Rep, 2017.

15.   Shimura, T., et al., *Association between circulating galectin-3 levels and the immunological, inflammatory and nutritional parameters in patients with colorectal cancer.* Biomed Rep, 2016. **5**(2): p. 203-7.

16.   Ross, J.S., et al., *Atherosclerosis and cancer: common molecular pathways of disease development and progression.* Ann N Y Acad Sci, 2001. **947**: p. 271-92; discussion 292-3.