ARIC Manuscript Proposal # 3218

PC Reviewed: 08/14/2018	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association between Galectin-3 with Arterial Stiffness: Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Galectin-3 and arterial stiffness

2. Writing Group:

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

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3. Timeline:

Analysis is anticipated to begin as soon as approval is obtained. The manuscript is to be prepared as soon as analyses are available. The analysis and manuscript preparation is anticipated to take place within one year of approval of the proposal.

4. Rationale:

Galectin-3 is a β-galactoside-binding lectin that is associated with pathophysiologic processes including inflammation, fibrosis and metabolic disorders. Recently, there has been increased interest in galectin-3 as a biomarker for cardiovascular disease as mounting evidence suggest that increased concentrations are associated with heart failure (Ho *J Am Coll Cardiol* 2012;60(14):1249-56), atrial fibrillation (Fashanu *Am Heart J* 2017;192:19-25), atherosclerosis (Madrigal-Matute *J Am Heart Assoc* 2014; doi: 10.1161/JAHA.114.000785) and adverse cardiovascular outcomes (Imran *Am J Cardiol* 2017;119:57-64, van Vark *J Am Heart Assoc* 2017; DOI: 10.1161/JAHA.116.003700). The role of galectin-3 in modulating pathways of inflammation and fibrosis makes it an interesting candidate in the study of myocardial (Lopez *Eur J Heart Fail* 2015;16:385-92) and vascular remodeling (Calvier *Artherioscler Thromb Vasc Biol* 2013;33:67-75), especially pertaining to patients with heart failure and hypertension. Though elevated biomarker levels are known to be associated with these conditions, and have been implicated in mortality and hospitalization in HF patients (Meijers *Am Heart J* 2014;167:853-60), the specific mechanism of how Galectin-3 plays a role in these diseases is less well understood.

One potential relationship may be between galectin-3 and arterial wall stiffness. Arterial stiffness as measured by aortic pulse wave velocity has been associated with increased risk for cardiovascular events and all-cause mortality (Ben-Shlomo *J Am Coll Cardiol* 2014;63:636-46, Mitchell *Circulation* 2010;122:1379-86, Vlachopoulos *J Am Coll Cardiol* 2010;55:1318-27). Progression of stiffness is a reflection of the complex interplay of age-related vessel remodeling with oxidative stress, inflammation and vascular strain from hypertension or metabolic derangements. However, arterial stiffness may precede the development of hypertension and may play a role in the pathogenesis of cardiovascular disease (Weisbrod *Hypertension* 2013;62:1105-10, Gailis *Hypertension* 2013;61:757-61). Increased arterial stiffening increases left

ventricular load, which over time, may lead to myocardial remodeling and impaired ventricular function (Chirinos *Hypertension* 2013;61:296-303).

In a previous study by Libhaber et. al. (Libhaber *Hypertension* 2015;65:1356-64), galectin-3 has been shown to be independently associated with aortic stiffness as measured by carotid-femoral pulse wave velocity (PWV) and aortic reflective wave index in 966 community participants with a mean age of 43.4 years. However, studies on this topic are limited. Data collected from ARIC include concentrations of galectin-3 on multiple visits as well as measurements of both central and peripheral arterial stiffness, arterial elastance and arterial-ventricular coupling. Thus, the ARIC study provides a unique opportunity to further explore and build upon findings from previous studies on the relationship between galectin 3 and arterial stiffness in a larger, older cohort population.

5. Main Hypothesis/Study Questions:

Hypothesis: Galectin-3 level is associated with arterial stiffness.

Study questions:

1. How is serum galectin-3 concentration associated with central and peripheral arterial stiffness and arterial elastance?

2. How is galectin-3 measurements associated with arterial-ventricular coupling?

3. How is change in galectin-3 levels over time associated with arterial stiffness, elastance and arterial-ventricular coupling?

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

This study will assess the association between galectin-3 (measured at visits 4 and 5) and indices of vascular function including arterial stiffness, arterial elastance index and arterial-ventricular coupling (all measured at visit 5).

Exposure

The major exposure of interest for this study will be galectin-3 levels. We will first examine cross-sectional association between galectin-3 levels at visit 5 with PWV measurements at visit 5. Additionally, Galectin-3 data from ARIC visit 4 will also be used to evaluate how temporal trends in galectin-3 is associated with arterial stiffness. To do this, we will perform analysis on the mean and percent change of galectin-3 concentrations at visits 4 and 5.

Outcomes

We will assess 3 major outcomes measures in this study:

1. Arterial stiffness was determined by PWV measured using an automated waveform analyzer at visit 5. Measure of central arterial stiffness will be based on carotid-femoral PWV (cfPWV) while measure for peripheral arterial stiffness will be based on femoral-ankle PWV (faPWV).
2. Arterial elastance index (Ea) is calculated as Ea = end-systolic pressure/stroke volume. End-systolic pressure was estimated as 0.9 × systolic BP, taken at the time of echocardiogram examination.
3. Arterial-ventricular coupling (a-v coupling), the ratio between the Ea and the LV elastance index (Elv), reflects cardiovascular hemodynamics through the interaction between the arterial system and the left ventricle.

Co-variates

Co-variables of interest include age, sex, race, systolic (SBP) and diastolic blood pressure (DBP) measurements, pulse pressure, hypertension status, treatment for hypertension, body mass index, diabetes status, LDL cholesterol, smoking status, history of coronary heart disease (CHD), estimated glomerular filtration rate (eGFR) at visit 5.

Exclusion Criteria

We will exclude individuals with race other than white/ black as well as participants with potential characteristics that may confound PWV readings: Minnesota code 8-1-2 with evidence of biased PWV waveforms, aortic aneurysms, abdominal aorta ≥5 cm, history of aortic or peripheral revascularization or aortic graft, aortic stenosis, moderate or greater aortic regurgitation, or BMI ≥40. We will also exclude individuals at visit 5 with a history of heart failure (HF) as elevated galectin-3 levels have been associated HF. Lastly, we will exclude individuals with missing data on exposure and outcome variables and co-variables of interest.

Statistical Analysis

Galectin-3 and Arterial Stiffness

First, we will describe the distribution of galectin-3 concentrations and will use the appropriate transformation (e.g. natural log, inverse normal) to correct for skewedness as needed. Galectin 3 levels will be treated both a continuous variable as well as a categorical variable divided in quartiles. To evaluate how galectin-3 levels relate to the outcome indices (PWV, Ea, and Ea/Elv), adjusted linear regression analysis will be used to assess for independent relationships between galectin-3 concentrations and outcome measures. Multiple models will be created using data from visit 5:

Model 1: Adjusting for age, sex, and race.
Model 2: Model 1 + adjusting for BMI, eGFR, heart rate, history of CHD, smoking, diabetes, elevated LDL cholesterol, and history of hypertension.

To assess whether arterial stiffness, elastance and a-v coupling measures are independent of blood pressure, additional step-wise models with adjustments for mean arterial pressure (MAP) and then pulse pressure will be created. Finally, as treatment for hypertension may affect outcome measures, sensitivity analysis will be performed on participants who have never received antihypertensive medications (though the number of participants who are treatment naïve to antihypertensive therapy at visit 5 may be very low).

Evaluating longitudinal levels of galectin-3

We will model change in galectin-3 levels in 3 ways.

1. We will model galectin-3 over time as the mean between visit 4 and 5, adjusting for baseline (visit 4) levels in our regression models.
2. We will create models with the percent change of galectin-3 levels between visits 4 and 5, adjusting for baseline (visit 4) levels for our regression analyses. Both mean and percent change will be analyzed as continuous variables and as categorical variables divided into quartiles. Adjusted linear regression analysis will be used to assess association between longitudinal change in galectin-3 concentration with each outcome measure.
3. We will categorize galectin-3 levels from visit 4 and visit 5 based on visit 4 tertile cutoffs (high, medium, low). We will then create cross-categories from visit 4 and visit 5 (ie high -> high, high -> medium, high -> low, medium -> high, etc). Cross-category groups will be compared using analysis of co-variance (ANCOVA) with outcome measures as the dependent variable and employing multiple co-variates as described above.

Adjustment of co-variates will be similar to the regression models as described above. In addition, as it is unclear how CHD events (including silent myocardial infarctions) between visits 4 and 5 may impact changes in galectin-3 levels, we will conduct separate analyses both with and without individuals who have documented CHD events between the two visits.

Limitations

1. Lack of PWV data from visit 4 precludes incident analysis of galectin-3 at visit 4 with arterial stiffness at visit 5.
2. Residual confounding may still be present due to observational nature of the study.

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

____ 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)?

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

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study *
___ 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.