ARIC Manuscript Proposal #4315

PC Reviewed: 9/12/23	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: A Metabolomic Study of Cardiac Dysfunction and Remodeling in Diabetes

b. Abbreviated Title (Length 26 characters): metabolites DM cardiac dysfunction

2. Writing Group [please provide a middle name if available; EX: Adam Lee Williams]:
Writing group members:

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

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3. Timeline: August – September 2023: ARIC P&P manuscript review and approval
September –March 2024: Data analysis and draft of the manuscript
April 2024 – Submit the manuscript to ARIC P&P and then to a peer-reviewed journal

4. Rationale:

Heart failure (HF) is one of the most common presentations of cardiovascular (CV) complications in diabetes (DM) and is associated with a 30% 1-year mortality among patients with DM.[1] HF can develop in individuals with DM without hypertension, coronary heart disease (CHD), or valvular heart disease. Recent research suggests that cardiac dysfunction and remodeling measured by echocardiography, including diastolic dysfunction, left atrial enlargement, left ventricular (LV) hypertrophy, and with or without elevated NP-pro BNP, was associated with up to 2.5-fold higher risk of HF among patients with DM. [2] Using the same measurements, we found that up to 10% of older adults (mean age 75 years) with pre-diabetes (pre-DM) had two or more cardiac dysfunction markers, and this group was also at a significantly increased risk of HF. These findings suggest the association between hyperglycemia and HF [3] and warrant research to lend insights into the novel biomarkers and pathways of cardiac dysfunction to aid in early intervention. A better understanding of the subclinical alterations in cardiac function and structure will facilitate strategies to reduce the risk of HF in older adults with diabetes before the advent of symptoms.

Molecular phenotyping is a promising approach for identifying individuals with DM and cardiac dysfunction while implicating novel biological pathways in HF pathogenesis, which can provide additional insights for therapeutic development. [4] Because metabolites represent a collective output of genetic and environmental factors and share a proximal relationship with clinical phenotypes, metabolomics profiling is a promise ng molecular tool for precision initiatives.[5 6] However, very few studies have evaluated the metabolic derangements that characterize cardiac dysfunction and remodeling in patients with pre-DM or DM. [2, 5] In previous metabolomics studies, arginine and branched-chain amino acid (BACC) metabolism, and fatty acid oxidation metabolism (e.g., medium- and long-chain acylcarnitines), and ketones are all potentially involved with the pathogenesis of HF [7, 8], but to what extent these metabolites is associated with the risk of HF in diabetes less known. Additionally, emerging research has shown sex differences in diabetic HF. DM is a more potent risk factor for HF development in women than men (5-fold risk in women with DM vs. two-fold risk in men with DM). [9] Women with DM have a higher prevalence of cardiac abnormalities, predominantly characterized by LV diastolic dysfunction than men. While men with DM are more likely to have LV hypertrophy and systolic dysfunctions. [10] Despite the sex heterogeneity of cardiac phenotypes in DM, our understanding of the sex differences in metabolic signatures with cardiac abnormalities in DM is limited.

5. Main Hypothesis/Study Questions:

Objective 1 To identify differentiating metabolites associated with cardiac dysfunction in older adults with and without DM in a cross-sectional study.

We hypothesize that serum metabolites, such as those involved in biological pathways of amino acids, particularly arginine, branched-chain amino acid (BACC) and aromatic amino metabolism, fatty acid oxidation metabolism, and ketone metabolism, are more strongly associated with cardiac dysfunction and remodeling in people with DM than those without DM.

Objective 2 To evaluate the associations between cardiac dysfunction-related metabolites and incident cardiac abnormalities, including subclinical left ventricular dysfunction and remodeling, and HF.

We hypothesize that cardiac dysfunction-related metabolites are associated with future risk of cardiac dysfunction and HF.

Our sub-hypothesis is that men and women with DM exhibit different metabolic signatures with cardiac dysfunction, and HF.

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).

Data and sample: We will use data from metabolome profiles based on visit 5 serum samples (n=4,000). Metabolomic profiling techniques and metabolite selection methods were described previously. [6]

DM status is measured by a self-reported DM diagnosis, fasting glucose (FG) 126 mg/dL, non-FG ≥200 mg/dL, hemoglobin A1c (HbA1c) >6.5%, or the use of insulin or oral antidiabetic medication. We also consider the confirmatory definition of diabetes by both elevated FG and A1c or any antidiabetic treatment.[11]

Pre-DM is measured by either FG 100-126 mg/DL,or HbA1c 5.7%-6.5% (ADA) or both We also consider IEC criterion of HbA1c 6.0% to 6.4% (IEC) and WHO FG levels of 100-126 mg/dL, separately to define pre-DM.

We will **exclude** prevalent cases of HF, or those with missing glycemic measures or metabolite data at visit 5.

Exposures: The exposures are untargeted serum metabolites measured by liquid chromatography mass spectrometry. We exclude metabolites that had unknown structure, missing rate >25%, CV >50% or Spearman correlation coefficient <0.3 in blind duplicate pairs. The remaining metabolites will be analyzed as continuous variables.

Outcome:

A composite cardiac dysfunction and remodeling outcome is defined by at least 2 echocardiographic abnormalities using data from visit 5, including LV remodeling, including, left ventricle hypotrophy, left atrial enlargement, and diastolic dysfunction (i.e., E/e'>13, E/A <1 and E-wave ≤50 cm/s, E/A>2, E/A<1 and right ventricle systolic pressure>35 mmHg, isovolumic relaxation time>100 ms, and E-wave deceleration time>240 ms).

We will also evaluate a more stringent definition includes ≥2 echocardiographic abnormalities plus elevated pro-BNP>125 pg/mL for BMI≤30 OR NT-proBNP>100 pg/mL for BMI>30, OR troponin T (TnT) >14 ng/L in women and > 22 ng/L in men.

Incident cardiac dysfunction and remodeling is defined as those without cardiac abnormalities at visit 5 but developed cardiac dysfunction and remodeling at visit 7 using echo data.

Incident HF is defined as a new diagnosis of definite or probable acute decompensated HF. Incident HF is based on HF hospitalization or HF death according to the ICD-9 or 10 codes obtained by active surveillance of all hospitalizations and death.
For those with data on cardiac function at the time of hospitalization, we will further classify HF as HF with preserved ejection fraction (HFpEF) by LVEF ≥50% and HF with reduced ejection fraction (HFrEF) by LVEF <50%.

Follow-up is available through December 31, 2020.

Analysis:

Metabolites will be natural logarithmic transformed before the analysis. Before association analyses, we will standardize the levels of metabolites by dividing each metabolite by its respective SD. We will impute the missing value of metabolites with half of the lowest detected value.

Each metabolite will be individually tested for association with cardiac dysfunction and remodeling within each group: euglycemia, prediabetes, or diabetes. We will also test each metabolite among people who had cardiac dysfunction and remodeling across three groups using logistic regression. In the models, we will account for age, race, sex, education, cigarette smoking, alcohol drinking, average systolic blood pressure, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate (eGFR) by CKD-EPI equation antihypertensive medications, and lipid-lowering medications. We will evaluate the standard and biomarker-included definition (i.e., with elevated pro-BNP or TnT) of cardiac dysfunction and remodeling. We will replicate the cross-sectional analysis in men and women, separately, to compare sex differences in individual metabolites associate with the outcomes.

For metabolites that are identified to be associated cardiac dysfunction and remodeling cross-sectionally, we will assess their association with the incident cardiac dysfunction and remodeling and HF using multivariable-adjusted Poisson or Cox regression models, following the aforementioned covariates and time-varying coronary artery disease. [6] We will further adjust CVD treatments, such as beta-blocker, ACE inhibitors, or ARBs in the model. If sex differences in metabolites and cardiac dysfunction and remodeling are shown in the cross-sectional analysis, we will perform sex-stratified prospective analysis to evaluate risk of cardiac abnormalities and HF and report the relative risk (women vs. men) of the outcomes.

We will conduct a series of sensitivity analyses, i.e., excluding people with hypertension, obesity, atrial fibrillation, or end-stage renal disease.

We will conduct exploratory analyses to assess association between metabolites and HFpEF and HFrEF separately. To account for the multiplicity of hypothesis tests in the metabolomics analysis, False Discovery Rate (FDR) adjusted p values will be calculated using the two-stage Benjamini and Hochberg step-up FDR-controlling procedure.

For internal validation, we will use ARIC visit 3 data to replicate metabolite-HF associations primarily and metabolite-subclinical cardiac abnormalities, secondarily.

We also consider replicating the analysis in an external cohort with similar metabolomic platform. Candidate cohorts include the Jackson Heart Study (JHS), the Hispanic Community Health Study (SOL), or the Women's Health Initiative (WHI).

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __x__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

__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)?

Yu B, Heiss G, Alexander D, Grams ME. "Associations Between the Serum Metabolome and All-Cause Mortality Among African Americans in the Atherosclerosis Risk in Communities (ARIC) Study." Am J Epidemiol. 2016;183(7):650-6.

Chandra A, Skali H, Claggett B, Solomon SD, Rossi JS, Russell SD, Matsushita K, Kitzman DW, Konety SH, Mosley TH, Chang PP**, Shah AM.** "Race- and Gender-Based Differences in Cardiac Structure and Function and Risk of Heart Failure" J Am Coll Cardiol. 2022;79(4):355-368.

Inciardi RM, Claggett B, Gupta DK, Cheng S, Liu J, Tcheugui JB Echouffo, Ndumele C, Matsushita K, Selvin E, Solomon SD, Shah AM, Skali H. "Cardiac Structure and Function and Diabetes-Related Risk of Death or Heart Failure in Older Adults."
J Am Heart Assoc. 2022;10:e022308. DOI: 10.1161/JAHA.121.022308

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _#2017.10_____)

___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.

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5. Zhang ZY, Marrachelli VG, Yang WY, et al. Diastolic left ventricular function in relation to circulating metabolic biomarkers in a population study. *Eur J Prev Cardiol*. Jan 2019;26(1):22-32. doi:10.1177/2047487318797395
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11. Prognostic Implications of Single-Sample Confirmatory Testing for Undiagnosed Diabetes. *Annals of Internal Medicine*. 2018;169(3):156-164. doi:10.7326/m18-0091 %m 29913486