ARIC Manuscript Proposal #2054

PC Reviewed: 12/11/12  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: The association of insulin resistance and glucose levels with cardiac structure and function in an older population without diabetes mellitus: The ARIC study

b. Abbreviated Title (Length 26 characters): Insulin Resistance and Echo

2. Writing Group:
Writing group members: Deepak K. Gupta, Orly Vardeny, Mauro Gori, Brian Claggett, Amil M. Shah, David Aguilar, Ervin Fox, Kunihiro Matsushita, Suma Konety, others welcome, Scott D. Solomon

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

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3. **Timeline:** Analysis will begin following proposal approval and availability of the visit 5 data. Anticipating completion of echocardiography of the ARIC Visit 5 cohort in 2013, a manuscript will be completed within 6 months of that date.

4. **Rationale:**

   Insulin resistance and impaired glucose metabolism may be risk factors for the development of heart failure (HF) in persons without diabetes mellitus (DM) and independent of progression to overt DM.\textsuperscript{1-13} Indeed, cross sectional analyses have demonstrated that insulin resistance and impaired glucose metabolism are associated with abnormalities of cardiac structure and function, including left ventricular hypertrophy, reduced left ventricular ejection fraction, and impaired diastolic function, even in the absence of symptoms.\textsuperscript{14-31} However, less is known about the relationship between insulin resistance, glucose levels, and cardiac structure and function specifically in the non-DM population. Furthermore, few studies have examined the relative contribution of insulin resistance and glucose levels in middle age to cardiac structure and function in the elderly.\textsuperscript{32, 33} Understanding how insulin resistance and glucose levels in middle and older ages relate to cardiac structure and function in the elderly will significantly contribute to clarifying the pathophysiology driving development of HF in the elderly population.

The Atherosclerosis Risk in Communities Study offers a unique opportunity to not only examine the cross sectional relationship between insulin resistance and glucose levels on cardiac structure and function in elderly non diabetics, but also the relative contribution of insulin resistance and glucose levels during middle age (visits 1-4) on cardiac structure and function in the elderly (visit 5). Furthermore, with this analysis we will be able to extend the existing literature regarding insulin resistance, glucose metabolism, and cardiac structure and function to both men and women as well as evaluate this relationship in whites and African-Americans.

5. **Main Hypothesis/Study Questions:** The primary objective of this study is to describe the relationships between insulin resistance and glucose levels on cardiac structure and function in elderly non-diabetics. We will also investigate whether insulin resistance and glucose levels in middle age are associated with cardiac structure and function at older age. To meet this goal, we have the following specific aims:

   1) To describe the cross sectional relationship between insulin resistance and glucose levels and cardiac structure and function in the elderly.
   2) To describe the longitudinal relationship between insulin resistance and glucose levels in middle age and cardiac structure and function in the elderly.
   3) To assess the relative strength of the association between insulin resistance and glucose levels in middle age vs. the elderly and cardiac structure and function in the elderly.
   4) To assess for interactions by gender and race regarding the relationship between insulin resistance and glucose levels and cardiac structure and function in the elderly.

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).**
This will be a study of ARIC cohort participants who undergo echocardiography during visit 5 (2011-2013). To be included in the analysis participants must have undergone echocardiography with acceptable image quality for analysis. Participants with prevalent heart failure, coronary heart disease, and diabetes mellitus at any of the visits will be excluded. Those with missing glucose and insulin values or data regarding risk factors for CVD will also be excluded.

**Primary Exposure Variable: Insulin Resistance**

There are several measures of insulin resistance and glucose levels available in ARIC, including the homeostasis model assessment insulin resistance (HOMA-IR) index, fasting glucose, fasting insulin, and hemoglobin A1c. The HOMA-IR index is a validated measure of insulin resistance that will be calculated from fasting insulin and fasting glucose values at Visits 1, 4 and 5 utilizing the following formula:

\[
\text{HOMA-IR} = \frac{\text{fasting insulin} \times \text{fasting glucose mg/dl}}{405}
\]

HOMA-IR values will be dichotomized at 2.5 as well as evaluated continuously following appropriate transformation if not normally distributed. Based upon the distribution of HOMA-IR values, alternate categorization, such as quartiles, may be considered.

In addition, insulin resistance may also be estimated from the individual components of HOMA-IR, namely fasting insulin or glucose levels. Additionally, hemoglobin A1c, even in non-diabetics has been demonstrated to carry prognostic value both for the development of overt diabetes mellitus, as well as adverse cardiovascular outcomes, and may also be a marker of insulin resistance, in addition to that of longer term glucose regulation. Therefore, these measures (fasting insulin levels, fasting glucose levels, and hemoglobin A1c) will also be examined as they relate to cardiac structure and function, both cross-sectionally at visit 5, as well as longitudinally from visits 1, 4, and 5 (insulin), visits 1-5 (glucose), and visits 2 and 5 (hemoglobin A1c). These variables will be evaluated categorically as well as continuously.

**Primary Outcome Variable: Cardiac structure and function**

Specifically, the relationship between insulin resistance and glucose levels and the following parameters of cardiac structure and function will be assessed:

1. left ventricular ejection fraction,
2. global LV systolic strain (longitudinal, circumferential, and radial),
3. left ventricular mass and geometry,
4. left ventricular diastolic function, and
5. left atrial size.

Clinical characteristics, echocardiographic cardiac structure and function, and biomarkers will be compared between insulin resistance and glucose groups. In particular, clinical variables to be evaluated include: age, gender, CVD risk factors, such as hypertension, dyslipidemia, smoking, BMI/obesity, stroke/TIA, peripheral arterial disease, atrial fibrillation/flutter, chronic kidney disease, anemia, COPD & asthma, and alcohol use; electrocardiographic left ventricular hypertrophy and QRS duration; heart rate, blood pressure (systolic, diastolic, mean arterial, and pulse pressure), height, weight, body surface area, WBC count, hemoglobin, red cell distribution
width, fasting glucose, HgbA1c, lipids, BNP, hsTnT; vascular stiffness by pulse wave velocity; and pulmonary function tests.

Echocardiographic variables to be evaluated include those related to cardiac structure: left ventricular (LV) size, LV wall thickness, LV mass, LV geometry, left atrial size and volumes, aortic root dimension, valvular disease, regional wall motion abnormalities, and right ventricular size. Parameters of cardiac function, including LV ejection fraction, right ventricular fractional area change, Doppler mitral inflow E and A wave peak velocities, E/A ratio, deceleration time, tissue Doppler systolic and diastolic indices at both the mitral and tricuspid annulus, as well as LV myocardial mechanics from speckle tracking imaging will be assessed. Noninvasive hemodynamic parameters including stroke volume, cardiac output, LV filling pressures, pulmonary vascular resistance, and pulmonary artery pressures will also be analyzed.

Categorical variables will be compared via χ2 or Fischer exact test, while continuous data will be compared between groups via Wilcoxon rank sum test or nonparametric trend tests as appropriate. P values < 0.05 will be considered significant.

Univariable and multivariable linear regression analysis will be used to assess associations between insulin resistance or glucose levels (independent) and echocardiographic characteristics (dependent) at visit 5. Adjustments for differences in clinical characteristics (based upon P <0.05 and/or clinically important covariates) will be performed.

Subsequently, to assess the relative contribution of insulin resistance and glucose levels from middle age on cardiac structure and function in the elderly, measures from visits 1-4 will be added to the multivariate linear regression model. Terms for insulin resistance and glucose levels (HOMA-IR, fasting glucose, fasting insulin, and hemoglobin A1c) in middle age will be entered into the primary multivariate linear regression models using visit 5 data. The measures from middle age will be included as individual covariates or as changes between visits or as average values across visits.

Limitations include baseline cardiac structure and function at visits 1, 2, and 4 is unknown. Euglycemic clamp is considered the “gold standard” measure of insulin resistance; however, this is a cumbersome and invasive procedure and is not typically conducted in epidemiological studies, and was not performed in ARIC. HOMA-IR, insulin, glucose, and hemoglobin A1c are surrogate measures of insulin resistance, which can lead to misclassification. Insulin levels were only measured at visits 1, 4, and 5. Hemoglobin A1c, which is a validated measure of longer term glucose levels, was only measured at visits 2 and 5. Additionally, it is probable that those with the highest insulin resistance or impaired fasting glucose in middle age developed overt diabetes mellitus, coronary heart disease, heart failure, and/or died prior to or did not attend visit 5, which may limit the ability to assess the association between insulin resistance in middle age and cardiac structure and function in the elderly.

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  _X___ No
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  __X__ 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)?

   MS Proposal #1883: Vardeny, O et al. The association of Insulin Resistance with Incident Heart Failure: the Atherosclerosis Risk in Communities (ARIC) study.

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

References


20. de las Fuentes L, Brown AL, Mathews SJ, Waggoner AD, Soto PF, Gropler RJ, Davila-Roman VG. Metabolic syndrome is associated with abnormal left ventricular diastolic function independent of left ventricular mass. *Eur Heart J.* 2007;28:553-559


24. Chinali M, Devereux RB, Howard BV, Roman MJ, Bella JN, Liue EF, Resnick HE, Lee ET, Best LG, de Simone G. Comparison of cardiac structure and function in American Indians with and without the metabolic syndrome (the strong heart study). *Am J Cardiol.* 2004;93:40-44


