ARIC Manuscript Proposal #3479

PC Reviewed: 10/8/19 **Status: _____** **Priority:2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
Association of Growth Differentiation Factor (GDF) 15 and Metabolic Outcomes: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
Growth differentiation factor (GDF) 15 and Metabolic Outcomes

2. Writing Group:
Writing group members: Justin B. Echouffo-Tcheugui, Natalie Daya, Kunihiro Matsushita, Chiadi Ndumele, Ron Hoogeveen, Mahmoud Al Rifai, Christie Ballantyne, Elizabeth Selvin; others welcome

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

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3. Timeline:
Analysis to begin immediately after the approval of the proposal, and submission of a draft of the manuscript for review to ARIC for review within 6 months.

4. Rationale:

Growth differentiation factor 15 (GDF-15) is a member of the transforming growth factor-β (TGF-β) cytokine superfamily.[1] In various human tissues including the adipose compartment, GDF-15 is primarily expressed in macrophages and epithelial cells.[2] GDF-15 is thought to be an adipokine, as its expression is positively associated with adiponectin production.[3]

The putative metabolic effects of GDF-15 have been described in a number of animal studies, [4–7] which point to a role in energy balance and glucose homeostasis. However, the exact role of GDF-15 in human metabolism remains poorly understood. In small human and clinic-based studies, high circulating GDF-15 levels have been observed among individuals with obesity or diabetes and GDF-15 levels are positively associated with fasting plasma glucose (FPG), glycosylated hemoglobin (HbA_{1c}), and insulin resistance.[8–11] Prior studies have also demonstrated a positive and independent association of GDF15 with risk cardiovascular disease among individuals with diabetes.[11,12]

Community-based studies have seldom investigated the association between GDF-15 and incident diabetes.[13,14] The few existing studies have a number of limitations, which include a limited scope as these mainly included Caucasian participants,[13,14] a relatively small sample size,[13] and somewhat contradictory results with respect to diabetes (with some studies suggesting an influence on the occurrence of diabetes, and one study suggesting the contrary).[13–15] It is important to clarify this relation given the potential clinical importance of GDF-15. Indeed, a number studies suggest that GDF-15 could be used as a robust and reliable marker of response to diabetes or obesity treatment, using metformin [16,17] or bariatric surgery.[18]

Using data from visit 6 (2016-2017) of the Atherosclerosis Risk in Communities (ARIC) study, we aim to assess the associations of GDF-15 with metabolic outcomes, including diabetes, obesity, and metabolic syndrome.

5. Main Hypothesis/Study Questions:

We hypothesize that among older individuals, plasma GDF-15 will be associated with an adverse metabolic risk profile. More precisely, circulating levels of GDF-15 will be positively associated with prevalent outcomes including: 1) diabetes, 2) obesity, and 3) metabolic syndrome.

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 criteria

Individuals included will be ARIC study participants who attended visit 6 (2016-2017), underwent a GDF-15 assessment, as well as assessment for the relevant cardiometabolic risk factors or outcomes. For the assessment of each of the incident outcome, we will exclude individuals with prevalent outcome at visit 6.

Exposure

Our exposure will be GDF-15 measured at visit 6 (2016-2017).

Outcomes

The primary outcome will be diabetes. We will also look at hyperglycemia measures continuously and characterize the association of GDF15 with cardiometabolic parameters. The outcomes will be cross-sectional and include the following:

- glycosylated hemoglobin (HbA_{1C})
- fasting plasma glucose (FPG),
- body mass index (BMI)
- waist circumference (WC),
- diabetes
- obesity
- metabolic syndrome among individuals without diabetes
- each component of metabolic syndrome (as detailed below)

Diabetes will be defined using the following criteria: self-reported history of doctor diagnosed diabetes mellitus or use of anti–diabetes mellitus medications, or $HbA_{1C} \geq 6.5\%$ or FPG≥126 mg/dL.
Obesity will be defined as a BMI ≥30 kg/m^2.
The metabolic syndrome will be defined using criteria proposed by the National Cholesterol Education Program—Adult Treatment Panel III.[19] The criteria include the following: high triglycerides [≥150 mg/dL] or use of lipid-lowering drugs, elevated systolic blood pressure (≥130 mm Hg) or diastolic blood pressure (≥85 mm Hg) or use of antihypertensive drugs, elevated blood glucose [≥100 mg/dL] or any use of medications for diabetes (insulin or oral glucose-lowering medications), low high-density lipoprotein (HDL)–cholesterol [<40 mg/dL in men and < 50 mg/dL in women], and WC ≥ 40 inches (men) or 35 inches (women).

Covariates

Depending on the outcome, the covariates will include the following: age, sex, race-center, income, alcohol use, smoking status, BMI, WC, systolic blood pressure (SBP), diastolic blood pressure (DBP), use of hypertension medications, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride, use of cholesterol-lowering medication, estimated glomerular filtration rate (eGFR), and history of cardiovascular disease (CVD).

Statistical analysis

We will examine the distribution of GDF-15 values, and if necessary transform the variable for the analyses. The baseline characteristics of participants will be presented by quartiles of GDF-15 concentrations.
We will use multivariable linear regression models to assess the association between GDF-15 and continuous outcomes, including FPG, HbA_{1C}, BMI and WC. We will use logistic regression to assess the odds of having diabetes, obesity or the metabolic syndrome by levels of GDF-15, included in models first as a continuous variable (SD increment) and then as a categorical (quartiles) variable. We will model GDF15 using linear and restricted cubic splines to more flexibly characterize the associations of GDF15 with the various metabolic parameters.
For the binary outcomes (diabetes, obesity and metabolic syndrome), we will use logistic regression, including GDF-15 as a continuous variable (SD increment) and then as a categorical variable (quartiles). We will perform spline analyses, to test for nonlinearity in the multivariable-adjusted associations of GDF-15 and each outcome.

In all the regression models (except for the metabolic syndrome outcome), we will include the following adjustment variables: age, sex, race-center, smoking status, alcohol use, eGFR, SBP, use of hypertension medications, ratio of total to HDL-cholesterol, history of CVD, BMI (for the diabetes outcomes), and diabetes status (for the obesity outcome). For the metabolic syndrome outcome, we will adjust for the following variables: age, sex, race-center, smoking status, alcohol use, and eGFR.
For all the outcomes, we will additionally adjust for physical activity and total energy intake, in a subsequent model.
For the diabetes outcome, we will test for the interaction by BMI, and for the obesity outcome, we will test for the interaction by diabetes status.

Limitations
The cross-sectional observational design limits our ability to draw temporal or causal conclusions from these data. We may have limited power to detect interactions and to examine associations in population subgroups. The older age range of this population may limit generalizability of the findings to younger populations.

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/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)?
None

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* _____)

_X__ 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 https://www2.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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