ARIC Manuscript Proposal #2521

PC Reviewed: 414/15 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Serum calcium and risk of diabetes: The Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Calcium & incident diabetes

2. Writing Group:
Writing group members: Mary R. Rooney, Pamela L. Lutsey, James S. Pankow, Shalamar Sibley, Elizabeth Selvin, Jared P. Reis
Other interested investigators welcome.

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline: Data analyses will begin immediately. Goal completion is mid-May 2015

4. Rationale:

Calcium is a mineral that is primarily found in the skeleton (99%) where it provides structural support and helps maintain calcium balance through extra-skeletal exchange.[1] Non-skeletal calcium serves a variety of functions throughout the body such as muscle contraction, vasoconstriction and vasodilation, and nerve transmission.[2] Calcium is primarily obtained through dietary intake of dairy products, dark green leafy vegetables, calcium fortified foods, or

supplementation.[3] Serum calcium levels are tightly regulated by 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], parathyroid hormone (PTH), and ionized calcium.[1]

Calcium has primarily been viewed in terms of bone health, but there is increasing interest as to its role in other diseases because of its tight regulation between the extracellular and intracellular space and within intracellular pools where it functions as an important second messenger and as a cofactor for some enzymes. An influx of calcium through calcium channels into pancreatic β-cells is required for insulin secretion.[4] Cross-sectional studies have found associations with altered calcium homeostasis and prevalent diabetes as well as metabolic syndrome.[5] Serum calcium levels have also been associated insulin resistance, fasting plasma glucose,[6,7] glucose intolerance[8] and beta cell function.[7] A case-control study found that individuals with type 2 diabetes had significantly higher serum calcium levels compared to controls.[9] To date, there have been three prospective studies that found elevated serum calcium was associated with higher diabetes risk.[10-12] One of these studies also found that those with the highest tertile of serum calcium change over a 7 year time-period had the highest risk of going on to develop T2DM.[12] However, these prospective studies did not collect data on serum vitamin D and parathyroid hormone levels. Two of the studies used participants of primarily European descent, which may limit their generalizability.

The calcium-sensing receptor (CASR) is primarily located in the parathyroid glands and kidneys, where it helps tightly regulate serum calcium levels through PTH secretion and calcium reabsorption.[13] In genetic-wide association studies, a single nucleotide polymorphism (rs1801725) within the CASR gene was associated with serum calcium levels in those of European ancestry.[14-15] It is not yet known if this gene variant is also related to serum calcium levels in blacks. If the SNP is associated with serum calcium, the association may provide insight into the altered calcium homeostasis and potentially diabetes development.

5. Main Hypothesis/Study Questions:

- Elevated serum calcium will be independently associated with greater risk of diabetes.
- SNP (rs1801725) found in CASR gene will be associated with greater risk of diabetes in whites. If this SNP is associated with serum calcium levels in blacks, we will test this hypothesis in blacks as well. We will also evaluate whether this SNP is an effect modifier of the association between serum calcium and diabetes risk.

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).

Study Design

Prospective cohort from visit 1

Inclusion/Exclusion

Participants with missing data on serum calcium and diabetes status as well as those with prevalent diabetes at visit 1 will be excluded. Participants who are neither African American nor white as well as African American participants at the Maryland and Minnesota centers will be excluded. Participants with incomplete diabetes follow-up information will also be excluded.

Variables

Exposures:

Primary: Total serum calcium was measured at visit 1. Approximately 40% of non-skeletal calcium is bound to proteins, primarily albumin and globulin.[1] As such, calcium will be corrected for albumin levels based upon the following equation: measured total calcium (mg/dL) + 0.8 [4.0 – serum albumin (g/dL)]. Albumin-adjusted calcium will be used for all analyses.

Secondary: SNP (rs1801725) within the calcium-sensing receptor (CASR) gene.

Outcome: Incident type 2 diabetes will be defined as fasting blood glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, self-report physician diagnosis, or current medication use for diabetes. Incident diabetes will be examined up to, and including, visit 4.

Main covariates: Age, race, center, sex, educational attainment, physical activity, smoking status, alcohol use, family history of diabetes, BMI, waist circumference

Potential effect modifiers: Age, race, sex, eGFR, rs1801725

Potential effect mediators: Parathyroid hormone, 25(OH)D, phosphorus

Data Analysis

Visit 1 will serve as baseline. Baseline participant data will be described by proportions or means stratified by serum calcium levels.

Cox proportional hazards regression will be used to analyze the association of serum calcium and incident diabetes. Model 1 will adjust for age, race, center, sex, and educational attainment. Model 2 will further adjust for behaviors, including physical activity, smoking status, alcohol use, and family history of diabetes. Model 3 will further adjust for BMI and waist circumference. In model 4 will additionally adjust, in separate models, for parathyroid hormone, 25(OH)D and serum phosphorus. Age, race, sex, and eGFR will be examined as effect modifiers of the association between serum calcium and incident diabetes. In whites (and blacks if rs1801725 is associated with calcium levels), we also will examine if the SNP (rs1801725) is associated with incident diabetes, and whether it modifies the association between serum calcium and diabetes.

In sensitivity analysis, we will exclude participants who use diuretics.

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? __X__ Yes ____ 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"? __X__ 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)?

#2340: 25(OH)D and incident diabetes. First author: Jared Reis

#2486: Parathyroid hormone and incident diabetes. First author: Jared Reis

#406: Magnesium and incident diabetes. First author: Linda Kao

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* _____)
__X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2009.17)

*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.

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