**ARIC Manuscript Proposal #2486**

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| **PC Reviewed: 1/13/15** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Parathyroid hormone and incident diabetes: The Atherosclerosis Risk in Communities (ARIC) Study

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

**2. Writing Group**: Jared P. Reis, Jim Pankow, Liz Selvin, Casey Rebholz, Pamela L. Lutsey. Others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __X__


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**3. Timeline**: Data analyses will begin immediately upon receiving data. Goal completion is Apr 2015.

**4. Rationale**:

Parathyroid hormone (PTH) helps to regulate circulating calcium concentrations by promoting resorption of calcium from the skeleton, suppressing urinary calcium loss, and enhancing the formation of calcitriol, the active metabolite of vitamin D. PTH levels are elevated in primary hyperparathyroidism and secondarily in vitamin D deficiency, chronic kidney disease, and other conditions.

Recent evidence has linked elevated PTH concentrations with insulin resistance, beta cell dysfunction, and dysglycemia [1-5], which may eventually lead to the development of diabetes. Indeed, studies of patients with primary hyperparathyroidism have shown a higher prevalence of diabetes compared to control populations [6-9]. While this evidence has suggested a role for PTH in the development of diabetes, these studies have primarily included small numbers of patients recruited from medical clinics. In addition, these studies have almost exclusively included white adults. Blacks are known to have a higher prevalence and incidence of diabetes [10, 11], higher concentrations of PTH [12], and differences in PTH-calcium metabolism compared to whites [13-15].

The objective of the current proposal is to examine the association of PTH with the incidence of diabetes in the ARIC study, a community-based cohort of white and black adults originally recruited in 1987-89.

**5. Main Hypotheses**:

1. Serum PTH will be positively associated with risk of diabetes.
2. The association between PTH and diabetes will be stronger among whites than among African Americans.
3. The positive association will remain after exclusion of those with suspected primary hyperparathyroidism and when analyses are restricted to those with normal kidney function.

**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 study from visit 2, when serum PTH was measured, with follow-up for incident diabetes.

Inclusion/Exclusion

Participants with prevalent diabetes and those missing data on PTH and diabetes status at visit 2 will be excluded, as will those who are neither African American nor white, and African Americans from the MN and MD centers (due to small numbers). We will further exclude those with no follow-up or incomplete incident diabetes information.

Variables

*Exposures*:

Primary: Serum PTH (measured in visit 2 serum). PTH will be used as a continuous variable, classified into categories according to the total population, and dichotomized by a clinical cut-point of 65 pg/mL.

*Outcome*:

- *Primary*: Incident type 2 diabetes will be identified at ARIC visits 3 and 4 by meeting any of the following four criteria: 1) fasting glucose level of at least 7.0

mmol/L (126 mg/dL); 2) nonfasting glucose of at least 11.1 mmol/L (200 mg/dL); 3) current use of diabetes medication; or 4) a positive self-reported physician diagnosis. Date of occurrence of diabetes will be assigned according to the method of Duncan and colleagues [16].

- *Secondary:* Incident self-reported physician diagnosis or use of diabetes medications from the annual telephone calls after visit 2 among persons without diabetes diagnosed at baseline.

If results are consistent across definitions, we will consider combining the two definitions to form a single diabetes outcome variable.

*Main covariates*: Age, race, center, sex, education, season of blood draw, physical activity, smoking status, alcohol use, family history of diabetes, serum calcium, phosphorus, 25(OH)D, BMI, and eGFR (modeled as ≥90, 60-89, and 15-59 ml/min/1.73 $m^2$). eGFR will be calculated using both creatinine and cystatin-C [17].

*Potential effect modifiers*: Race, sex, eGFR, 25(OH)D.

Data analysis

Visit 2 will serve as baseline for the current analysis. Visit 2 participant characteristics will be described using means and proportions stratified by levels of parathyroid hormone.

For the primary analysis we will use multivariable Cox proportional hazards regression models to estimate hazard ratios (HR) and their corresponding 95% confidence intervals (CI) according to baseline PTH. We will use restricted cubic splines to characterize the continuous association of PTH with diabetes, evaluate the potential for a threshold effect, and aid in the identification of the most appropriate exposure representation [18]. Our first model will adjust for age, sex, race-center, season, education, physical activity, smoking status, alcohol use, eGFR, and family history of diabetes. Model 2 will additionally adjust for serum calcium, phosphorus, and 25(OH)D. Model 3 will adjust for model 1 covariates in addition to BMI.

Multiplicative interaction terms will be used to evaluate whether race, sex, BMI, eGFR, or 25(OH)D modify associations between PTH and risk of incident diabetes. Given inherent interest due to few available large studies of racially diverse populations, we will report race-stratified results, regardless of whether a significant race-interaction is present.

In sensitivity analyses, we will exclude those with suspected primary hyperparathyroidism (elevated PTH and serum calcium) and restrict our analyses to those with normal kidney filtration function at visit 2 (eGFR ≥90 ml/min/1.73 $m^2$).

**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

__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: Race, Vitamin D Binding Protein Gene Polymorphisms, 25-Hydroxyvitamin D, and Incident Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study. *Jared P Reis, Erin D Michos, Elizabeth Selvin, James Pankow, Pamela L Lutsey*

Published paper: Parathyroid hormone concentration and risk of cardiovascular diseases: The Atherosclerosis Risk in Communities (ARIC) Study. *Aaron R Folsom, Alvaro Alonso, Jeffrey R Misialek, Erin D Michos, Elizabeth Selvin, John H Eckfeldt, Josef Coresh, James S Pankow, Pamela L Lutsey*

**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**
**__X__ A. primarily the result of an ancillary study**

**2009.17 (Lutsey PI)**
- "Serum vitamin D and cardiovascular disease risk in the biethnic ARIC cohort"

**___ 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.

**References**


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12. **Gutierrez, O.M., et al., *Racial differences in the relationship between vitamin D, bone mineral density, and parathyroid hormone in the National Health and Nutrition Examination Survey.* Osteoporos Int, 2011. 22(6): p. 1745-53.**
13. **Bell, N.H., et al., *Evidence for alteration of the vitamin D-endocrine system in obese subjects.* J Clin Invest, 1985. 76(1): p. 370-3.**
14. **Cosman, F., et al., *Resistance to bone resorbing effects of PTH in black women.* J Bone Miner Res, 1997. 12(6): p. 958-66.**

15. **Kleerekoper, M., et al.,** ***Reference data for bone mass, calciotropic hormones, and biochemical markers of bone remodeling in older (55-75) postmenopausal white and black women.*** **J Bone Miner Res, 1994. 9(8): p. 1267-76.**
16. **Duncan, B.B., et al.,** ***Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study.*** **Diabetes, 2003. 52(7): p. 1799-805.**
17. **Inker, L.A., et al.,** ***Estimating glomerular filtration rate from serum creatinine and cystatin C.*** **N Engl J Med, 2012. 367(1): p. 20-9.**
18. **Harrell, F.E., Jr., K.L. Lee, and B.G. Pollock,** ***Regression models in clinical studies: determining relationships between predictors and response.*** **J Natl Cancer Inst, 1988. 80(15): p. 1198-202.**