ARIC Manuscript Proposal #2222

PC Reviewed: 9/10/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Parathyroid hormone and the risk of incident hypertension: The Atherosclerosis Risk in Communities Study (ARIC)

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

2. Writing Group: Lu Yao, Weihong Tang, Erin D. Michos, Aaron R. Folsom, James S. Pankow, Elizabeth Selvin, Alvaro Alonso, Pamela L Lutsey, Others welcome

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

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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 June 2014.

4. Rationale: Parathyroid hormone (PTH) is a regulatory factor in bone health and mineral homeostasis, and the level of PTH is mainly altered by vitamin deficiency and kidney disease[1]. Recently, PTH is thought to have vascular effects, and may therefore alter blood pressure. Endothelial dysfunction is thought to underlie PTH's vascular properties. Specifically, PTH may increase serum levels of endothelin-1 and interleukin-6[2, 3], and may stimulate the vascular smooth muscle cells to produce factors including collagen and beta-1 integrin which could, in turn, increase the stiffness of the peripheral vasculature [4]. Also, PTH may increase renin release and activate the renin-angiotension

system [5, 6]; a process mediated by renal 1-alpha-hydroxylase and resultant changes in 1, 25(OH_2)D^7.

Most epidemiologic evaluations of the relation between PTH and hypertension were cross-sectional [8-10], and only a few prospective cohort studies have examined the relation [11, 12]. Taylor et al reported that PTH was associated with higher risk of incident self-reported hypertension among 481 male professionals; however, some important factors, such as plasma vitamin D, were not considered, and the results might not be extrapolated to general population given a very high prevalence (greater than 50%) of kidney stones in this study sample[12]. Another prospective study of members of the Intermountain Healthcare system also found that PTH was positively related to hypertension in older people (mean age:63 years) over an average of 2 years of follow-up (max:7.5 years), but as all information came from medical records the author's ability to adjust for confounders was limited[11].

In addition, racial differences in the association between levels of PTH and vitamin D have been identified [13-15]. These studies raise interest in whether there are racial differences in the association between PTH and risk of hypertension.

5. Main Hypothesis/Study Questions:

To better evaluate the relation between PTH and hypertension, therefore, we will take advantage of data from ARIC, a large, bi-racial, population-based cohort, and will prospectively examine the association between PTH and the risk of incident hypertension. We hypothesize that PTH is positively associated with risk of incident hypertension. Given inherent interest, we will also evaluate whether race is an effect-modifier of the association between PTH and incident hypertension. Additionally, we will carefully consider vitamin D, renal function, and other factors which may be mediators of the relation between PTH and hypertension.

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 beginning at Visit 2, when PTH was measured.

Inclusion/Exclusion

Whites and African Americans who attended Visit 2 and had measures of PTH will be included. Among these participants, we will exclude those who at visit 2 had prevalent cardiovascular disease, or prevalent hypertension (self-reported hypertension, anti-hypertensive medication use, or systolic/diastolic blood pressure ≥140/90 mmHg) as well

as those who are neither African American nor white, and African Americans from the MN and MD centers.

Variables:

Exposures: PTH measured in Visit 2 serum.

Outcomes:

- *Primary*: Incident hypertension, defined as systolic/diastolic blood pressure ≥ 140/90 mmHg or self-reported antihypertensive medication use at ARIC visits 3 and 4.
- *Secondary:* Incident self-reported hypertension based on ARIC annual follow-up phone calls.

Confounders: age, race-center, sex, educational levels, estimated glomerular filtration rate (eGFR) using CKD-EPI equation[16], season of exam, physical activity, smoking status, alcohol intake, body mass index , C-reactive protein.

Potential effect modifiers: age, race-center, sex, and eGFR.

Possible mediators (if not as modifiers): 25 hydroxyvitamin D [25 (OH) D], serum calcium, serum phosphorous, eGFR.

Data analysis

We will describe the characteristics at Visit 2 (baseline) stratified by levels of PTH.

Cox proportional hazards regression will be performed to explore the relation between race-specific PTH and risk of incident hypertension. We will use restricted cubic splines to examine the continuous association between PTH and hypertension. This will aid in determining the best way to model PTH. Our first model will adjust for age, sex, race-center and season. Model 2 will additionally adjust for educational level, physical activity, smoking status, alcohol intake, and body mass index. In additional models we will further adjust for 25(OH)D, eGFR, serum calcium, and serum phosphorous.

We will explore interaction by race-center, age, sex, and eGFR. Stratified results will be reported, as appropriate. Regardless of whether a statistically significant interaction is present, race-stratified results will be presented, given inherent interest.

Additional sensitivity analyses will be conducted restricting our analysis to participants with normal kidney function (eGFR ≥90 ml/min/1.73 m^2), and excluding people with primary hyperparathyroidism defined by high levels of both serum PTH and calcium (PTH >65 and calcium > 10.2 mg/dL).

Since the primary outcome, incident hypertension, was only ascertained at Visits 3 and 4, the precise time-to-event is unknown. Therefore, we will perform a sensitivity analysis using logistic regression to evaluate the association between PTH and incident hypertension.

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)?

MP2184. Parathyroid hormone and CVD (First author: Aaron Folsom)

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"

2009.16 (Selvin PI)
- "Short-term markers of glycemia and long-term outcomes"
- Cystatin C, which is used to calculate eGFR, was measured as part of this grant.

___ 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:

1. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol.* 2008; 52: 1949-1956.
2. Rashid G, Bernheim J, Green J, Benchetrit S. Parathyroid hormone stimulates endothelial expression of atherosclerotic parameters through protein kinase pathways. *Am J Physiol Renal Physiol.* 2007; 292: F1215-8.
3. Isales CM, Sumpio B, Bollag RJ, Zhong Q, Ding KH, Du W, Rodriguez-Commes J, Lopez R, Rosales OR, Gasalla-Herraiz J, McCarthy R, Barrett PQ. Functional parathyroid hormone receptors are present in an umbilical vein endothelial cell line. *Am J Physiol Endocrinol Metab.* 2000; 279: E654-62.
4. Perkovic V, Hewitson TD, Kelynack KJ, Martic M, Tait MG, Becker GJ. Parathyroid hormone has a prosclerotic effect on vascular smooth muscle cells. *Kidney Blood Press Res.* 2003; 26: 27-33.
5. Pilz S, Tomaschitz A. Role of vitamin D in arterial hypertension. *Expert Rev Cardiovasc Ther.* 2010; 8: 1599-1608.
6. Grant FD, Mandel SJ, Brown EM, Williams GH, Seely EW. Interrelationships between the renin-angiotensin-aldosterone and calcium homeostatic systems. *J Clin Endocrinol Metab.* 1992; 75: 988-992.
7. Fitzpatrick LA, Bilezikian JP, Silverberg SJ. Parathyroid hormone and the cardiovascular system. *Curr Osteoporos Rep.* 2008; 6: 77-83.

8. Snijder MB, Lips P, Seidell JC, Visser M, Deeg DJ, Dekker JM, van Dam RM. Vitamin D status and parathyroid hormone levels in relation to blood pressure: a population-based study in older men and women. *J Intern Med.* 2007; 261: 558-565.
9. Zhao G, Ford ES, Li C, Kris-Etherton PM, Etherton TD, Balluz LS. Independent associations of serum concentrations of 25-hydroxyvitamin D and parathyroid hormone with blood pressure among US adults. *J Hypertens.* 2010; 28: 1821-1828.
10. Jorde R, Sundsfjord J, Haug E, Bonaa KH. Relation between low calcium intake, parathyroid hormone, and blood pressure. *Hypertension.* 2000; 35: 1154-1159.
11. Anderson JL, Vanwoerkom RC, Horne BD, Bair TL, May HT, Lappe DL, Muhlestein JB. Parathyroid hormone, vitamin D, renal dysfunction, and cardiovascular disease: dependent or independent risk factors? *Am Heart J.* 2011; 162: 331-339.e2.
12. Taylor EN, Curhan GC, Forman JP. Parathyroid hormone and the risk of incident hypertension. *J Hypertens.* 2008; 26: 1390-1394.
13. Fuleihan GE, Gundberg CM, Gleason R, Brown EM, Stromski ME, Grant FD, Conlin PR. Racial differences in parathyroid hormone dynamics. *J Clin Endocrinol Metab.* 1994; 79: 1642-1647.
14. Isakova T. Racial differences in parathyroid hormone levels in CKD. *Nephrol Dial Transplant.* 2012; 27: 2616-2617.
15. Gutierrez OM, Farwell WR, Kermah D, Taylor EN. 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: 1745-1753.
16. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS, CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* 2012; 367: 20-29.