ARIC Manuscript Proposal #4291

PC Reviewed: 07/11/23 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Serum Sodium, Potassium, Magnesium, Calcium, and Phosphate Levels and Risk of Fracture in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
Sodium, Potassium, Magnesium, Calcium, and Phosphate & Fracture

2. Writing Group:
Writing group members: Atsuko Uehara, Yejin Mok, Kunihiro Matsushita, Pamela Lutsey, Junichi Ishigami, others welcome.

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

First author: Atsuko Uehara
Address:

Phone: Fax:
E-mail: auehara4@jhu.edu

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).
Name: **Junichi Ishigami**
Address: 2024 E Monument St, Baltimore, MD 21205

Phone: (410) 955-4156 Fax:
E-mail: jishiga1@jhu.edu

3. Timeline:
Data analysis and manuscript preparation will be done in the next 12 months.

4. Rationale:
Bone fracture is a major public health concern associated with increased mortality, disability, and health care costs[1,2,3]. In the United States, the incidence of osteoporosis-related fracture is predicted to increase from 2.1 million in 2005 to 3 million in 2025 due to the growing elderly

population[4]. Since a number of fracture cases are considered preventable, identification of risk factors is crucial to implement early preventive interventions (e.g., osteoporosis treatment and non-pharmacological interventions) in those at high risk[5]. Furthermore, if risk factors are modifiable, such knowledge may unravel a novel preventive target to reduce the risk of fracture.

Electrolytes are essential for mineral and bone metabolism and may be relevant to the risk of fracture. Calcium and phosphate are the main components of bone in the form of matrix and hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$]), and affect bone turnover primarily through the regulation of endocrine hormones such as fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH)[6,7]. A study combining data from the Dutch Rotterdam Study and the US Osteoporotic Fractures in Men study (MrOS) reported that higher levels of serum phosphate were associated with the risk of fracture,[13] although the study population mostly consisted of people of Caucasian ancestry.

Further, evidence from in vitro and animal studies suggests that other electrolytes such as sodium, potassium, and magnesium also interact with bone metabolism[8-11] and can affect bone mass[12]. Previous studies have examined serum magnesium[14] or sodium level[15] and the risk of fracture, but both study populations were comprised exclusively of Caucasian men, and neither study accounted for mineral and bone markers (e.g., FGF23, and PTH). To our knowledge, no study has investigated the association of multiple components of serum electrolytes with the risk of fracture in a racially diverse cohort.

In this proposal, we will explore whether baseline serum levels of sodium, potassium, magnesium, calcium, and phosphate are associated with the incidence of hospitalization with fracture using data from the Atherosclerosis Risk in Communities (ARIC) Study.

5. Main Hypothesis/Study Questions:
Electrolyte imbalances are independently associated with risk of fracture.

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 analysis beginning at ARIC visit 2 (main analysis: Analysis 1) and visit 5 (secondary analysis: Analysis 2).

Inclusion/Exclusion Criteria: Analysis 1 will include all ARIC study participants who attended visit 2 when serum electrolyte levels and other covariates of interest were measured. Since the risk of fracture is particularly high in older adults, Analysis 2 will include participants who attended visit 5 to examine the association of interest among older cohort. We will exclude individuals with a history of fracture prior to visit 2 (Analysis 1) and visit 5 (Analysis 2), as appropriate, and non-black/non-white participants.

Exposures: Exposures of interest will be serum levels of sodium (Na), potassium (K), magnesium (Mg), calcium (Ca), and phosphate (P).

Outcome: Primary outcome will be fractures requiring hospitalization. These events will be ascertained using the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM), codes on hospital discharge records regardless of diagnostic position (Table 1). We will include fractures identified by the presence of ICD-9-CM codes 733.1x, 733.93 to 733.98, or 800 to 829. We will exclude fractures associated with transport accidents (E800-848), fractures of toes, finger, and skull or face (ICD-9-CM codes 733.94, 800, 801, 802, 803, 815, 816, 817, 825, or 826)[16]. Since the ARIC Study transitioned to ICD-10-CM codes starting November 1, 2015, these ICD-9-CM codes will be converted to ICD-10-CM using the General Equivalence Mappings (GEMs) developed by the Centers for Medicare & Medicaid Services[17].

Table 1: ICD-9-CM codes relevant to fracture

ICD-9CM	
733.1x	Pathologic fracture
733.93-733.98	Stress fracture
804	Multiple fractures involving skull or face with other bones
805	Fracture of vertebral column without mention of spinal cord injury
806	Fracture of vertebral column with spinal cord injury
807	Fracture of rib(s) sternum larynx and trachea
808	Fracture of pelvis
809	Ill-defined fractures of bones of trunk
810	Fracture of clavicle
811	Fracture of scapula
812	Fracture of humerus
813	Fracture of radius and ulna
814	Fracture of carpal bone(s)
818	Ill-defined fractures of upper limb
819	Multiple fractures involving both upper limbs and upper limb with rib(s) and sternum
820	Fracture of neck of femur
821	Fracture of other and unspecified parts of femur
822	Fracture of patella
823	Fracture of tibia and fibula
824	Fracture of ankle
827	Other multiple and ill-defined fractures of lower limb
828	Multiple fractures involving both lower limbs lower with upper limb and lower limb(s) with rib(s) and sternum
829	Fracture of unspecified bones

Other variables of interest and covariate: Covariates will include age, sex, race, body mass index (BMI), smoking status (current vs. former/never), alcohol consumption (current vs. former/never), diabetes, hypertension, postmenopausal status (in women), prevalent coronary heart disease, specific medication use (glucocorticoids, antidepressants, thiazide diuretics, bisphosphonates, loop diuretics, hormone replacement therapy [in women], benzodiazepines, proton pump inhibitors, and thiazolidinedione, see Table 2), estimated glomerular filtration rate

($eGFR_{Cr}$; calculated using the CKD-EPI [CKD epidemiology Collaboration] 2009 equation), serum albumin, 25-hydroxyvitamin D, PTH, and FGF23.

Table 2: Medication codes

Medication name	Relevance to fracture risk	Medication code
Glucocorticoids	↑risk of fracture	220000, 221000
Antidepressants	↑risk of fracture via fall	580000, 581000, 581600, 582000, 583000
Thiazide diuretics	↓Na, K, Mg level	376000
Bisphosphonates	↓risk of fracture	300420
Loop diuretics	↓K, Mg level	372000
Menopausal hormonal therapy	↓risk of fracture	240000, 249900, 249930
Benzodiazepines	↑risk of fracture via fall	571000, 602010, 721000
Proton pump inhibitors	↑risk of fracture, ↓Mg level	492700
Thiazolidinediones	↑risk of fracture	276070

Statistical Analysis Plan: Baseline characteristics will be compared by Na, K, Ca, Mg, and P categories using chi-square tests for categorical variables and ANOVA for continuous variables. The level of electrolytes will be treated as categorical variables, according to quintiles, and the middle quintiles of each electrolyte will be set as a reference group. We will also treat these variables as continuous variables. For both Analysis 1 and Analysis 2, we will estimate the cumulative incidence of fracture using Kaplan Meier curves. We will estimate hazard ratios (HRs) by using multivariable Cox proportional hazards models. We will test the following three models. Model 1 will be adjusted for age, gender, and race*center. Model 2 will be further adjusted for BMI, smoking status (current vs. former/never), alcohol consumption (current vs. former/never), diabetes, hypertension, postmenopausal status (in women), prevalent coronary heart disease, specific medication use (glucocorticoids, antidepressants, thiazide diuretics, bisphosphonates, loop diuretics, hormone replacement therapy [in women], benzodiazepines, proton pump inhibitors, and thiazolidinedione. Model 3 will be further adjusted for $eGFR_{Cr}$, serum albumin, 25-hydroxyvitamin D, PTH, and FGF23. We will perform subgroup analysis in predetermined covariates of age (e.g., <65 vs. >= 65 years), sex (male vs. female), and race (white vs. black).

Sensitivity analysis: We will examine the association between electrolyte imbalances and specific subtypes of fracture (upper limb, lower limb, vertebral, or hip). Second, we will use clinical thresholds for individual electrolytes (Table 3), based on the normal range in the general population.

Table 3: Clinical thresholds for low- and high- levels of electrolytes

	Low	Normal	High	References
Na	<135 mEq/L	135-145 mEq/L	>145 mEq/L	18
K	<3.5 mEq/L	3.5-5.3 mEq/L	>5.3 mEq/L	19
Mg	<0.75 mmol/L (<1.8 mg/dL)	0.75-0.95 mmol/L (1.8-2.3 mg/dL)	>0.95 mmol/L (>2.3 mg/dL)	20
Ca	<2.1 mmol/L (<8.4 mg/dL)	2.1-2.6 mmol/L (8.4-10.4 mg/dL)	>2.6 mmol/L (>10.4 mg/dL)	21, 22

P	<2.5 mg/dL	2.5-4.5 mg/dL	>4.5 mg/dL	23

Limitations: No bone mineral density assessment, residual confounding, population restricted to Black and White adults in the community

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __x__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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)?

To date, we are not aware of any manuscript that has examined the association of serum electrolyte levels with risk of fracture. ARIC Manuscript Proposal #2371 examined the association of CKD with the risk of fracture. However, this study did not consider any electrolytes or mineral and bone markers in their models.

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 https://sites.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.

References

1. Richmond J, Aharonoff GB, Zuckerman JD, Koval KJ. Mortality risk after hip fracture. J Orthop Trauma. 2003;17(1):53-56. doi:10.1097/00005131-200301000-00008
2. Braithwaite RS, Col NF, Wong JB. Estimating hip fracture morbidity, mortality and costs. J Am Geriatr Soc. 2003;51(3):364-370. doi:10.1046/j.1532-5415.2003.51110.x
3. Orsini LS, Rousculp MD, Long SR, Wang S. Health care utilization and expenditures in the United States: a study of osteoporosis-related fractures. Osteoporos Int. 2005;16(4):359-371. doi:10.1007/s00198-004-1694-2
4. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007;22(3):465-475. doi:10.1359/jbmr.061113
5. Mitchell PJ, Chem C. Secondary prevention and estimation of fracture risk. Best Pract Res Clin Rheumatol. 2013;27(6):789-803. doi:10.1016/j.berh.2013.11.004
6. Wilczynski C, Camacho P. Calcium use in the management of osteoporosis: continuing questions and controversies. Curr Osteoporos Rep. 2014;12(4):396-402. doi:10.1007/s11914-014-0234-z
7. Katsumata K, Kusano K, Hirata M, et al. Sevelamer hydrochloride prevents ectopic calcification and renal osteodystrophy in chronic renal failure rats. Kidney Int. 2003;64(2):441-450. doi:10.1046/j.1523-1755.2003.00126.x
8. Barsony J, Kleess L, Verbalis JG. Hyponatremia Is Linked to Bone Loss, Osteoporosis, Fragility and Bone Fractures. Front Horm Res. 2019;52:49-60. doi:10.1159/000493237
9. Bushinsky DA, Riordon DR, Chan JS, Krieger NS. Decreased potassium stimulates bone resorption. Am J Physiol. 1997;272(6 Pt 2):F774-F780. doi:10.1152/ajprenal.1997.272.6.F774

10. Rude RK, Gruber HE, Norton HJ, Wei LY, Frausto A, Kilburn J. Reduction of dietary magnesium by only 50% in the rat disrupts bone and mineral metabolism. Osteoporos Int. 2006;17(7):1022-1032. doi:10.1007/s00198-006-0104-3
11. Rude RK, Gruber HE, Norton HJ, Wei LY, Frausto A, Mills BG. Bone loss induced by dietary magnesium reduction to 10% of the nutrient requirement in rats is associated with increased release of substance P and tumor necrosis factor-alpha. J Nutr. 2004;134(1):79-85. doi:10.1093/jn/134.1.79
12. Verbalis JG, Barsony J, Sugimura Y, et al. Hyponatremia-induced osteoporosis. J Bone Miner Res. 2010;25(3):554-563. doi:10.1359/jbmr.090827
13. Campos-Obando N, Koek WNH, Hooker ER, et al. Serum Phosphate Is Associated With Fracture Risk: The Rotterdam Study and MrOS. J Bone Miner Res. 2017;32(6):1182-1193. doi:10.1002/jbmr.3094
14. Kunutsor SK, Whitehouse MR, Blom AW, Laukkanen JA. Low serum magnesium levels are associated with increased risk of fractures: a long-term prospective cohort study. Eur J Epidemiol. 2017;32(7):593-603. doi:10.1007/s10654-017-0242-2
15. Jamal SA, Arampatzis S, Harrison SL, et al. Hyponatremia and Fractures: Findings From the MrOS Study. J Bone Miner Res. 2015;30(6):970-975. doi:10.1002/jbmr.2383
16. Lutsey PL, Norby FL, Ensrud KE, et al. Association of Anticoagulant Therapy With Risk of Fracture Among Patients With Atrial Fibrillation. JAMA Intern Med. 2020;180(2):245-253. doi:10.1001/jamainternmed.2019.5679
17. https://www.cms.gov/Medicare/Coding/ICD10/ICD-10-MS-DRG-Conversion-Project
18. Seay NW, Lehrich RW, Greenberg A. Diagnosis and Management of Disorders of Body Tonicity-Hyponatremia and Hypernatremia: Core Curriculum 2020. Am J Kidney Dis. 2020;75(2):272-286. doi:10.1053/j.ajkd.2019.07.014
19. Palmer BF, Clegg DJ. Physiology and Pathophysiology of Potassium Homeostasis: Core Curriculum 2019 [published correction appears in Am J Kidney Dis. 2022 Nov;80(5):690]. Am J Kidney Dis. 2019;74(5):682-695. doi:10.1053/j.ajkd.2019.03.427
20. Reddy ST, Soman SS, Yee J. Magnesium Balance and Measurement. Adv Chronic Kidney Dis. 2018;25(3):224-229. doi:10.1053/j.ackd.2018.03.002
21. Peacock M. Calcium metabolism in health and disease. Clin J Am Soc Nephrol. 2010;5 Suppl 1:S23-S30. doi:10.2215/CJN.05910809
22. Cooper MS, Gittoes NJ. Diagnosis and management of hypocalcaemia [published correction appears in BMJ. 2008 Jun 28;336(7659): doi: 10.1136/bmj.a334]. BMJ. 2008;336(7656):1298-1302. doi:10.1136/bmj.39582.589433.BE
23. Koumakis E, Cormier C, Roux C, Briot K. The Causes of Hypo- and Hyperphosphatemia in Humans. Calcif Tissue Int. 2021;108(1):41-73. doi:10.1007/s00223-020-00664-9