ARIC Manuscript Proposal # 1450r

PC Reviewed: 12/9/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Potassium and magnesium levels and intake and their associated risk of prediabetes and diabetes: The Atherosclerosis Risk in Communities Study.

b. Abbreviated Title (Length 26 characters): K+ and Mg++ and Diabetes Risk

2. Writing Group:

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

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3. Timeline: Data analysis and manuscript preparation will be performed over the next eight months.

4. Rationale: The effects of the diabetes epidemic on the health of Americans and on the healthcare systems are substantial, affecting over 8% of Americans and costing over $174 billion in 2007.[1] Diabetes prevention is important for reducing morbidity and mortality in Americans as well as for reducing overall healthcare costs. A key component to diabetes prevention is encouraging weight loss for those that are overweight and obese, as obesity is a key risk factor for diabetes. However, weight is not the only risk factor for diabetes, and there are other metabolic and nutritional risk factors for diabetes that may be modified to reduce the risk of developing diabetes.

Hypokalemia is thought to be associated with hyperglycemia, primarily through impairment of insulin secretion.[2] This has been studied mostly in subjects on thiazide diuretics, [3] but not all studies have found a relationship between thiazides and the development of hyperglycemia or diabetes.[4] ACE-inhibitors have been found, in some studies, to prevent hyperglycemia, possibly through their effect of raising potassium levels.[5] The association of potassium level, independent of drug effects, with risk of prediabetes and diabetes has not been well-studied.

Hypomagnesemia has also been associated with increased risk of diabetes [6,7] and poorer glycemic control in those with established diabetes.[8] Magnesium and potassium levels are known to be affected by medications, including thiazide diuretics. One study using early data from ARIC found an independent association of magnesium levels on risk of diabetes, controlling for potassium levels and use of thiazides,[6] but not all studies have taken these relationships into account. This same study also looked at dietary magnesium intake and found no relationship between this exposure and risk of diabetes; [6] however, other studies have found an inverse association between dietary magnesium intake and risk of diabetes. [9] Increased dietary intake of potassium has been linked to lower risk of cardiovascular outcomes,[10] including stroke,[11] but its association with diabetes risk has not been well studied.

5.Main Hypothesis/Study Questions: Using ARIC data available to date, we will study the association of serum potassium and magnesium levels, as well as levels of dietary potassium and magnesium intake, on glycemia and the risk of prediabetes and diabetes, in patients that are free from these conditions at baseline.

Specific Aim 1: To determine the relationship between serum potassium and magnesium levels and fasting glucose levels in 13774 non-diabetic ARIC participants.

Hypothesis: Lower potassium and lower magnesium levels are associated with higher fasting glucose levels

Specific Aim 2: To determine the risk of prediabetes and diabetes with serum potassium and magnesium levels.

Hypothesis: There will be a higher adjusted risk of prediabetes/diabetes associated with lower serum potassium and magnesium levels.

Specific Aim 3: To determine the risk of prediabetes and diabetes with levels of dietary potassium and dietary magnesium intake.

Hypothesis: There will be a higher adjusted risk of prediabetes/diabetes associated with lower dietary potassium and magnesium intake.

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 using Atherosclerosis Risk in Communities (ARIC) data

Exclusion criteria:
Subjects with prediabetes and/or evidence of diabetes, based on fasting blood glucose of ≥ 100 mg/dl or ≥ 126 mg/dl (depending on the analysis being performed), or non-fasting glucose ≥ 140mg/dl or ≥ 200 mg/dl (depending on the analysis being performed), clinical diagnosis of diabetes reported by subjects, and/or use of medications for diabetes as reported by patients; subjects with missing information on diabetes status (glucose levels), missing serum potassium or magnesium levels, or subjects with elevated serum creatinine (≥ 1.7mg/dl) at Visit 1. For the analyses using dietary potassium and magnesium as the primary exposures, subjects with missing nutritional information at Visit 1 will be excluded from these analyses

Primary outcome measures:
1) development of prediabetes, defined as a fasting glucose of ≥ 100mg/dl and < 126 mg/dl or a non-fasting glucose ≥ 140 mg/dl and < 200 mg/dl at any follow-up visit, and/or a 2-hour post-challenge glucose of ≥ 140mg/dl and < 200 mg/dl, determined at Visit 4, with no evidence of diabetes at any prior visit,

2) development of diabetes, defined as a clinical diagnosis reported by subjects and/or use of medications for diabetes as reported by patients, and/or biochemical evidence of diabetes, defined as a fasting glucose ≥ 126 mg/dl or a non-fasting glucose ≥ 200mg/dl at any follow-up visit, and/or a 2-hour post-challenge glucose of ≥ 200mg/dl, determined at Visit 4,

3) a combined endpoint of the 2 outcomes above.

Exposure measures:
1) Serum potassium level measured at Visit 1 will be modeled as a continuous variable as well as an ordinal or categorical variable, with levels divided into quartiles based on the range of values for all the subjects

2) Serum magnesium level measured at Visit 1 will be modeled as a continuous variable and/or used as an ordinal or categorical variable with levels divided into quartiles based on the range of values for all the subjects

3) Dietary potassium intake will be modeled as an ordinal or categorical variable, with levels divided into quartiles based on the range of values for all subjects.

4) Dietary magnesium intake will be modeled as an ordinal or categorical variable, with levels divided into quartiles based on the range of values for all subjects.

Data analysis:
1) Baseline characteristics of subjects with different outcomes (normoglycemia, prediabetes, diabetes) will be compared—using $\chi 2$ tests for categorical variables and standard normal (z) tests for continuous variables.

2) A cross-sectional analysis using data from Visit 1 will be performed using linear regression to determine if there is a significant relationship between fasting glucose levels and serum potassium and magnesium levels among non-diabetics, as well as between fasting glucose levels and dietary potassium and magnesium intake levels among nondiabetics. Covariates to be considered will include:

> age of subject, race, BMI, baseline fasting glucose, family history of diabetes, presence of absence of hypertension, blood pressure, physical activity level, use of diuretics, use of ACE-I/ARBs, use of beta-blockers, and calcium levels.

3) Cox proportional hazards models will be used to evaluate the hazard ratio for development of prediabetes and/or diabetes in relation to the main exposure variables. Linear interpolation and a time-to-diabetes variable, developed in a previous ARIC study,[12] will be used to determine the time a subject developed diabetes based on the glucose levels measured at Visits 2, 3, and 4. Serum potassium levels and magnesium levels will be used as the primary exposures, as well as dietary potassium and magnesium intake levels in separate analyses. Covariates to be considered will be:

> age of subject, race, BMI, baseline fasting glucose, family history of diabetes, presence of absence of hypertension, blood pressure, physical activity level, use of diuretics, use of ACE-I/ARBs, use of beta-blockers, and calcium levels.

Measurement Error:
The main exposures of these analyses, potassium and magnesium, are subject to measurement error due to biological and laboratory variability, as well as factors affecting specimen collection.[13] The use of one measurement, at Visit 1, for each exposure introduces bias to our measurement of the association between our outcome and these exposures.[14] Studies have been done with NHANES and ARIC data which take into account this intra-individual variability in measurements.[13, 15, 16] Lacher, et al evaluated variability in laboratory measurements for subjects participating in NHANES III who had repeat measurements taken soon after their initial evaluation. This study found potassium to have within-person variability of 5.4%.[13] In our regression models, we will take into account these measurement errors to address this bias and to try to better define the true association between our outcome and exposures, using methods similar to those used by Kottgen, et al.[17]

Sensitivity analyses:
The outcome of diabetes will be followed after Visit 4 using AFU data from telephone follow up.

Other sensitivity analyses will be considered as well.

Limitations:
1) There will not be accurate biochemical diagnoses of prediabetes and diabetes at visits other than at Visit 4, which is the only visit at which a 2 hour glucose challenge test was administered. We, therefore, could be missing subjects with the outcomes at the other visits.

2) Other limitations: residual confounding, measurement error, lack of power to detect effect modification

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 ICTDER03 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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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)?

Serum potassium is associated with metabolic syndrome, Andrew, ME, 02-18-1998

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 at http://www.cscc.unc.edu/aric/forms/

12. 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.

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