

Serum and Dietary Potassium and Risk of Incident Type 2 Diabetes Mellitus

The Atherosclerosis Risk in Communities (ARIC) Study

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Background: Serum potassium levels affect insulin secretion by pancreatic β -cells, and hypokalemia associated with diuretic use has been associated with dysglycemia. We hypothesized that adults with lower serum potassium levels and lower dietary potassium intake are at higher risk for incident diabetes mellitus (DM), independent of diuretic use.

Methods: We analyzed data from 12 209 participants from the Atherosclerosis Risk in Communities (ARIC) Study, an ongoing prospective cohort study, beginning in 1986, with 9 years of in-person follow-up and 17 years of telephone follow-up. Using multivariate Cox proportional hazard models, we estimated the hazard ratio (HR) of incident DM associated with baseline serum potassium levels.

Results: During 9 years of in-person follow-up, 1475 participants developed incident DM. In multivariate analyses, we found an inverse association between serum po-

tassium and risk of incident DM. Compared with those with a high-normal serum potassium level (5.0-5.5 mEq/L), adults with serum potassium levels lower than 4.0 mEq/L, 4.0 to lower than 4.5 mEq/L, and 4.5 to lower than 5.0 mEq/L had an adjusted HR (95% confidence interval [CI]) of incident DM of 1.64 (95% CI, 1.29-2.08), 1.64 (95% CI, 1.34-2.01), and 1.39 (95% CI, 1.14-1.71), respectively. An increased risk persisted during an additional 8 years of telephone follow-up based on self-report with HRs of 1.2 to 1.3 for those with a serum potassium level lower than 5.0 mEq/L. Dietary potassium intake was significantly associated with risk of incident DM in unadjusted models but not in multivariate models.

Conclusions: Serum potassium level is an independent predictor of incident DM in this cohort. Further study is needed to determine if modification of serum potassium could reduce the subsequent risk of DM.

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SEVERAL LINES OF EVIDENCE point to hypokalemia as a possible risk factor for type 2 diabetes mellitus (DM). First, in analyses of data collected from randomized controlled trials of thiazide diuretics, serum potassium was inversely related to glucose—an effect that is blunted by oral potassium supplementation.¹ Second, experimental studies provide biological plausibility by showing that thiazide-induced hypokalemia leads to diminished insulin secretion.^{2,3} Third, in some randomized control trials, angiotensin-converting enzyme inhibitors (ACEIs), which increase serum potassium as well as have several other effects along with their effects on blood pressure, were associated with a decreased risk of DM.⁴ Most recently, a reanalysis of data from the Systolic Hypertension in Elderly Program (SHEP) Study identified hypokalemia as a mediator of thiazide-related risk of incident DM.⁵ However, to our knowledge, no epidemiologic studies have evaluated the risk of DM associated with serum po-

tassium levels independent of thiazide use. We, therefore, analyzed data from the Atherosclerosis Risk in Communities (ARIC) Study to test the hypothesis that adults with lower serum potassium levels within the “normal range” are at higher risk for incident DM, even without diuretic use. We also sought to determine whether higher dietary potassium intake was associated with lower DM risk. If a low serum potassium level is indeed a risk factor for DM, then a strategy to increase serum potassium—either with medications, supplements, or dietary modifications—might represent a novel approach to DM prevention.

METHODS

The ARIC Study is a prospective cohort study involving 15 792 adults aged 45 to 65 years at the baseline visit, recruited based on population-based probability sampling in 1986 to 1989 from 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi; the northwest suburbs of Minneapolis, Minnesota; and Washing-

ton County, Maryland. Participants visited the clinic every 3 years through 1998 for approximately 9 years of follow-up. They were then followed yearly for an additional 8 years (through 2006), primarily through telephone contact. Details of the design and conduct of the ARIC study have been published previously.⁶ Institutional review boards at each of the participating institutions approved the study.

STUDY PARTICIPANTS

We excluded participants sequentially from this analysis if, at the baseline visit, they had DM (n=1870), defined as (1) a fasting glucose level of 126 mg/dL or higher, (2) a nonfasting glucose level of 200 mg/dL or higher, (3) participant report of a physician diagnosis, or (4) use of medications to treat DM.⁷ We excluded participants with missing baseline DM information or missing serum potassium levels (n=148); those with a high serum potassium level (>5.5 mEq/L) (n=156); persons with ethnicity other than white or African American (n=44); and those who had fasted less than 8 hours (n=257), had a serum creatinine level higher than 1.7 mg/dL (n=75), or had missing information on incident DM or covariates outside of the main exposure (n=1033). These exclusions produced a cohort of 12 209 participants for this analysis. For the dietary analyses, we further excluded participants if they had missing or incomplete dietary information (n=364), other missing covariates (n=117), or extreme values in total daily caloric intake. We defined extreme values for total daily caloric intake as less than 600 or more than 4000 kcal/d for females and less than 800 or more than 5000 kcal/d for males (n=204), producing a cohort of 11 530 for the dietary analyses. (To convert glucose and potassium to millimoles per liter, multiply by 0.555 and 1.0, respectively. To convert creatinine to micromoles per liter, multiply by 88.4.)

SERUM AND DIETARY POTASSIUM LEVELS

The primary exposure of interest was serum potassium. Blood samples were aliquoted, centrifuged, frozen, and stored at -70°C in central laboratories.⁶ Serum potassium from the baseline visit was measured with a direct electrochemical technique on undiluted serum.⁸ Dietary potassium intake was estimated from an interviewer-administered, modified version of the 61-item food frequency questionnaire developed by Willett et al.⁹ Dietary potassium intake was analyzed as milligrams of intake per total kilocalories consumed per day.

INCIDENT TYPE 2 DM

The main outcome was a diagnosis of DM assessed in participants at each of the 3 follow-up visits. A visit-based definition of DM was defined, as in the "Study Participants" subsection, by any 1 of the following 4 conditions: (1) a fasting glucose level of 126 mg/dL or higher, (2) a nonfasting glucose level of 200 mg/dL or higher, (3) participant report of a physician diagnosis, or (4) use of medications to treat DM.⁷ Since those with DM at the baseline visit were excluded, participants who met these criteria at subsequent visits were considered to have incident DM. For this definition, the date of onset of DM was estimated by linear interpolation using fasting glucose values at the visit at which DM was ascertained and the immediately preceding visit.⁷

To confirm the robustness of the main findings, we conducted analyses with an alternative definition of incident DM and longer duration of follow-up. First, we limited the definition of DM to self-report of physician diagnosis or self-reported use of DM medications through visit 4 (year 9 of follow-

up), thereby excluding cases of undiagnosed DM. This interview-based approach allowed us to extend follow-up beyond the final in-person clinic visit to include data from annual telephone calls. Thus, the second analysis defined incident DM as self-report of physician diagnosis or self-reported use of DM medications through 2006 (years 17-20 of follow-up). For both the first and second analyses, the date of onset of DM was defined as the date of the interview in which DM was first reported.

COVARIATES

Potential confounding factors included different demographic variables, anthropometric values, laboratory values, and use of medications that were assessed at the baseline visit. We included the following covariates in our models: age; sex; race; center; body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared); waist circumference; serum magnesium, calcium, and creatinine levels; physical activity level; parental history of DM; presence of hypertension; average of systolic blood pressure readings from second and third measurements; fasting glucose and insulin levels; income; and of use of β -blockers, diuretics, and ACEIs. Demographic information and information on parental history, physical activity, and medication use were obtained during an in-person interview; anthropometric and laboratory measurements were obtained in a standardized fashion and by trained personnel.^{8,10}

STATISTICAL ANALYSIS

Serum potassium levels were categorized into 4 clinically meaningful groups: lower than 4.0 mEq/L, 4.0 to lower than 4.5 mEq/L, 4.5 to lower than 5.0 mEq/L, and 5.0 to 5.5 mEq/L. We determined and compared the mean (SD) or frequency of baseline characteristics of the study population by categories of potassium level using 1-way analysis of variance F tests for continuous variables and Pearson χ^2 tests for categorical variables. We performed multivariate linear regression to assess cross-sectional relationships between serum potassium and glyce-mic parameters, including fasting glucose and fasting insulin tests and homostatic model assessment of insulin resistance (HOMA-IR),¹¹ after adjustments for potential covariates. We used Cox proportional hazard regression models to investigate the association between baseline serum potassium levels and incident DM after adjustment for potential confounding variables, chosen based on a priori knowledge, using the highest potassium category (5.0-5.5 mEq/L) as the reference group. The proportional hazards assumption was tested on categories of serum potassium and all potential confounders using log-log survival curves and goodness-of-fit tests. We also conducted analyses using serum potassium levels as a continuous variable and categorizing measures into quintiles and deciles to ensure that the categorization by clinically relevant cut-points was robust. We tested for interaction between serum potassium level and age, sex, race, BMI, and income, as categorical variables on risk of DM. In the analyses of dietary potassium, we also used Cox regression models. We categorized potassium intake per kilocalorie (kcal) into quartiles with cutoffs of less than 1.37 mg/kcal, 1.37 to less than 1.63 mg/kcal, 1.63 to less than 1.93 mg/kcal, and 1.93 mg/kcal or more and used the highest quartile of intake (≥ 1.93 mg/kcal) as the reference group. We also used dietary potassium intake as a continuous variable and as a categorical variable by itself, with total kilocalorie intake as a separate, independent variable.

Finally, we performed other sensitivity analyses using subgroups of participants based on their use of medications, excluding participants who were prescribed diuretics, as well as

Table 1. Baseline Characteristics of 12 209 ARIC Participants by Serum Potassium Level at Baseline^a

Characteristic	Serum Potassium Level, mEq/L				P Value ^b
	<4.0	4.0 to <4.5	4.5 to <5.0	5.0 to 5.5	
Participants, No.	1619	4903	4178	1509	
Age	54.0 (5.77)	53.7 (5.65)	54.0 (5.76)	54.0 (5.64)	.04
African American race	45.3	25.8	14.2	8.2	<.01
Female sex	70.0	57.5	50.8	49.0	<.01
Family history of diabetes mellitus	24.0	22.7	22.5	21.3	.35
BMI	28.6 (5.90)	27.4 (5.12)	26.9 (4.70)	26.1 (4.23)	<.01
Waist circumference, cm	97.9 (14.58)	95.9 (13.25)	95.5 (12.84)	93.4 (12.42)	<.01
Hypertension present	63.6	29.2	22.6	19.7	<.01
Systolic BP, mm Hg	124 (20)	119 (18)	119 (17)	118 (16)	<.01
Serum potassium level, mEq/L	3.68 (0.25)	4.22 (0.14)	4.67 (0.14)	5.17 (0.16)	<.01
Serum magnesium level, mEq/L	1.58 (0.17)	1.63 (0.15)	1.66 (0.14)	1.69 (0.14)	<.01
Serum calcium level, mg/dL	9.71 (0.44)	9.70 (0.41)	9.81 (0.41)	9.96 (0.40)	<.01
Serum creatinine level, mg/dL	1.06 (0.18)	1.08 (0.18)	1.10 (0.18)	1.12 (0.18)	<.01
Fasting glucose level, mg/dL	99.07 (10.27)	97.81 (9.23)	98.83 (8.93)	99.84 (8.85)	<.01
Fasting insulin level, μ U/mL	13.72 (111.21)	11.10 (8.17)	10.76 (7.77)	9.67 (6.12)	<.01
Leisure activity	2.31 (0.58)	2.38 (0.56)	2.42 (0.56)	2.47 (0.55)	<.01
β -Blocker use	16.1	9.0	7.7	8.0	<.01
Diuretic use	45.5	13.9	7.9	5.7	<.01
ACEI use	3.2	2.5	2.4	2.1	.28
Dietary potassium intake, mg/kcal	1.63 (0.43)	1.65 (0.42)	1.68 (0.41)	1.70 (0.41)	<.01
Combined family annual income, \$ ^c					
<5000-11 999	27.4	17.9	14.2	11.6	<.01
12 000-24 999	25.5	20.8	19.2	15.0	
25 000-49 999	31.4	37.0	38.6	39.1	
>50 000	15.6	24.3	28.1	34.3	

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure.

SI conversion factors: To convert calcium, glucose, magnesium, and potassium to millimoles per liter, multiply by 0.25, 0.555, 0.50, and 1.0, respectively. To convert insulin to picomoles per liter, multiply by 6.945. To convert creatinine to micromoles per liter, multiply by 88.4.

^aValues are given as mean (SD) for continuous variables and percentages for categorical variables.

^bP values are from 1-way analysis of variance or χ^2 test of overall difference.

^cIncome is reported in 1986 US dollars.

excluding those who were prescribed diuretics, β -blockers, ACEIs, and potassium or magnesium supplements. Finally, we performed subsidiary analyses with additional covariates, including estimated glomerular filtration rate, HOMA-IR, smoking status (never, current, former), and amount of alcohol consumption.

Tests of significance were 2-tailed, with an α level of .05. We performed all analyses using SAS statistical software (version 9.1.3; SAS Institute, Cary, North Carolina).

RESULTS

The mean age of participants at baseline was 54 years, 56% were female, and 22% were African American. Their mean BMI was 27, and the mean serum potassium level was 4.4 mEq/L (range, 2.5-5.5 mEq/L).

Table 1 shows the characteristics of the participants based on their serum potassium level. These groups differed significantly for all baseline covariates assessed except for percentages of participants with parental history of DM and use of ACEI, which was low for all groups. A higher percentage of African Americans and females had potassium levels in the lower range of the spectrum. Lower potassium levels were associated with higher BMI, larger waist circumference, lower serum magnesium levels, higher fasting insulin levels, higher use of β -blockers, and higher use of diuretics. Multivariate cross-

sectional analyses revealed a significant inverse relationship between serum potassium and fasting insulin levels. A nonlinear association was found between serum potassium and fasting glucose levels (Table 1).

During the first 9 years of follow-up, 1475 adults developed DM (according to the in-person visit-based definition). The crude incidence rate of DM was highest in adults with serum potassium levels lower than 4.0 mEq/L (24.6 per 1000 person-years); adults with higher potassium levels had progressively lower rates of DM (**Table 2**). The hazard ratio (HR) of incident DM, adjusted for age, sex, race, and center, was also highest for those with a potassium level lower than 4.0 mEq/L with an HR of 2.05 (95% confidence interval [CI], 1.64-2.56) compared with those with serum potassium levels of 5.0 to 5.5 mEq/L (Table 2).

After adjustments for age; sex; race; center; BMI; waist circumference; serum magnesium, calcium, and creatinine levels; physical activity; parental history of DM; presence of hypertension; average systolic blood pressure of second and third measurements; fasting glucose and insulin levels; income; and use of β -blockers, diuretics, and ACEIs, the Cox proportional hazard models revealed an increased risk of developing DM with lower potassium levels. When compared with those with a high-normal serum potassium level (5.0-5.5 mEq/L), adults with se-

Table 2. Crude Rates of Incident Diabetes Mellitus (DM) and Partially Adjusted Hazard Ratios (HRs) by Serum Potassium Level at Baseline

Crude Rate and Partially Adjusted HR of Incident DM	Serum Potassium Level, mEq/L			
	<4.0	4.0 to <4.5	4.5 to <5.0	5.0 to 5.5
Incident cases of DM ^a	284 (120)	616 (485)	456 (402)	119 (111)
Person-years	11 567	37 113	32 073	11 816
Rate/1000 person-years	24.6	16.6	14.2	11.8
Age-, sex-, race-, and center-adjusted HR (95% CI)	2.05 (1.64-2.56)	1.52 (1.25-1.85)	1.37 (1.12-1.68)	1 [Reference]

Abbreviation: CI, confidence interval.

SI conversion factor: To convert potassium to millimoles per liter, multiply by 1.0.

^aPatients not prescribed diuretics.

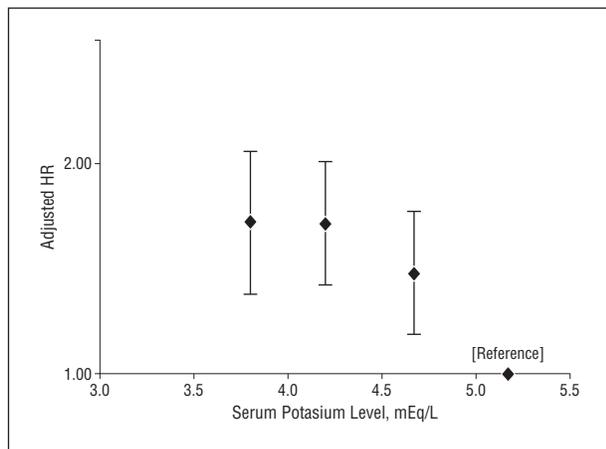


Figure 1. Adjusted relative hazard ratios (HRs) for incident diabetes mellitus (DM) by serum potassium at baseline. Relative HRs are adjusted for age; sex; race; center; body mass index; waist circumference; serum magnesium, calcium, and creatinine levels; physical activity levels; parental history of DM; presence of hypertension; systolic blood pressure (mean of second and third measurements); fasting glucose and fasting insulin levels; income; and use of β -blockers, diuretics, and angiotensin-converting enzyme inhibitors. The error bars indicate 95% confidence intervals. Results are plotted at the medians of the potassium categories (3.8, 4.2, 4.7, and 5.2 mEq/L). To convert potassium to millimoles per liter, multiply by 1.0.

rum potassium levels lower than 4.0 mEq/L, 4.0 to lower than 4.5 mEq/L, and 4.5 to lower than 5.0 mEq/L had an adjusted HR of incident DM of 1.64 (95% CI, 1.29-2.08), 1.64 (95% CI, 1.34-2.01), and 1.39 (95% CI, 1.14-1.71), respectively (P value for trend $<.001$) (**Figure 1**). A similar inverse relationship was found when serum potassium level was categorized differently according to quintiles or deciles, with all HRs being statistically significant. When serum potassium was used as a continuous variable, its coefficient revealed an inverse association with DM risk that was statistically significant ($\beta = -0.27$; $P < .001$). We included estimated glomerular filtration rate (in milliliters per minute per 1.73 m²), HOMA-IR, and alcohol consumption as continuous variables, and smoking status as a categorical covariate, all of which had no effect on the pattern of association.

In the stratified analyses by age, sex, BMI, and household income, the inverse relationship between serum potassium level and DM risk remained in fully adjusted models. The association was also similar among African Americans and whites with no significant statistical interaction ($P > .50$). Adjusted HRs of incident DM for Afri-

can Americans with a serum potassium level lower than 4.0 mEq/L, 4.0 to lower than 4.5 mEq/L, and 4.5 to lower than 5.0 mEq/L were 2.42 (95% CI, 1.29-4.53), 2.14 (95% CI, 1.16-3.97), and 1.87 (95% CI, 1.00-3.49), respectively, compared with those with a serum potassium level of 5.0 to 5.5 mEq/L; adjusted HRs of incident DM for whites for the same potassium groups were 1.46 (95% CI, 1.09-1.96), 1.50 (95% CI, 1.20-1.88), and 1.28 (95% CI, 1.03-1.59).

SENSITIVITY ANALYSES

To confirm the robustness of the main findings, we conducted 2 types of supplementary analyses: (1) we used the interview-based definition of DM, and (2) we conducted subgroup analyses based on use of medications.

When using the interview-based definition of DM during the main 9-year study period, 607 participants reported newly diagnosed DM, and there was a significant association between diagnosis of incident DM and serum potassium level. Among these participants, when compared with those with high-normal serum potassium level (5.0-5.5 mEq/L), adults with a serum potassium level lower than 4.0 mEq/L, 4.0 to lower than 4.5 mEq/L, and 4.5 to lower than 5.0 mEq/L had adjusted HRs of incident DM of 1.46 (95% CI, 0.99-2.16), 1.39 (95% CI, 0.99-1.95), and 1.47 (95% CI, 1.05-2.06), respectively (**Table 3**). Using our interview-based definition over the entire 17-year study period, 2552 adults reported a diagnosis of DM. The relationship between incident DM and baseline serum potassium during this longer follow-up period was still significant, with serum potassium levels lower than 5.0 mEq/L being associated with a significantly higher risk of incident DM compared with participants with a serum potassium level of 5.0 to 5.5 mEq/L; however, as with the shorter follow-up period using the interview-based definition of DM, the graded association was no longer as evident (Table 3).

For participants who were prescribed diuretics ($n = 1835$) and those not prescribed diuretics ($n = 10\,373$), we found similar trends in both groups, with a higher risk of developing DM among those with lower potassium levels. Point estimates for the HRs were higher for each category of potassium level for those prescribed diuretics compared with those not prescribed diuretics; however, 95% CIs for each category overlapped for the 2 groups of participants (**Figure 2** and Table 3), with wide

Table 3. Summary of Results From Multivariate Analyses Assessing the Relationship Between Risk of Incident Diabetes Mellitus (DM) and Serum Potassium Levels

Model (Total No.; Cases of Incident DM)	Incident DM ^a Adjusted HR (95% CI) According to Serum Potassium Level, mEq/L		
	<4.0	4.0 to <4.5	4.5 to <5.0
Main model (n=12 209; 1475)	1.64 (1.29-2.08)	1.64 (1.34-2.01)	1.39 (1.14-1.71)
Participants not prescribed medications (n=9353; 930) ^b	1.57 (1.14-2.16)	1.48 (1.17-1.88)	1.38 (1.09-1.74)
Participants not prescribed diuretics (n=10 373; 1118)	1.41 (1.06-1.88)	1.51 (1.21-1.87)	1.35 (1.09-1.67)
Participants prescribed diuretics (n=1835; 357)	2.91 (1.41-6.00)	2.85 (1.38-5.88)	1.93 (0.92-4.08)
Participant self-report of DM, 9 y (n=12 209; 607)	1.46 (0.99-2.16)	1.39 (0.99-1.95)	1.47 (1.05-2.06)
Participant self-report of DM, 17 y (n=12 209; 2552)	1.24 (1.04-1.48)	1.29 (1.11-1.49)	1.31 (1.13-1.51)

Abbreviations: CI, confidence interval; HR, hazard ratio.

SI conversion factor: To convert potassium to millimoles per liter, multiply by 1.0.

^aThe HRs and CIs were adjusted for age; sex; race; center; body mass index; waist circumference; serum magnesium, calcium, and creatinine levels; physical activity; parental history of DM; presence of hypertension; systolic blood pressure; fasting glucose and insulin levels; income; and use of β -blockers, diuretics (unless indicated otherwise), and angiotensin-converting enzyme inhibitors (ACEIs). A potassium level of 5.0 to 5.5 mEq/L was the reference category for each comparison.

^bParticipants not taking β -blockers, ACEIs, diuretics, or potassium or magnesium supplementation.

95% CIs for the group prescribed diuretics, likely owing to the smaller sample size.

After excluding all participants who were prescribed diuretics, β -blockers, ACEIs, and potassium or magnesium supplements, there was a graded increase in HR of incident DM with lower serum potassium levels. When compared with those with high-normal serum potassium levels (5.0-5.5 mEq/L), adults with serum potassium levels lower than 4.0 mEq/L, 4.0 to lower than 4.5 mEq/L, and 4.5 to lower than 5.0 mEq/L had adjusted HRs of incident DM of 1.57 (95% CI, 1.14-2.16), 1.48 (95% CI, 1.17-1.88), and 1.38 (95% CI, 1.09-1.74), respectively (Table 3).

DIETARY ANALYSES

Participants included in the dietary analyses had a mean dietary potassium intake of 2655 mg/d (recommended daily intake is 4700 mg/d) with a mean intake per kilocalorie of 1.66 mg/kcal. As expected, the correlation between serum potassium levels and dietary intake of potassium was modest ($r=0.06$; 95% CI, 0.04-0.08). We performed bivariate (unadjusted) analysis between dietary potassium intake and incident DM, which revealed a significant graded increase in the risk of incident DM with lower dietary potassium intake. Participants in the lowest to higher quartiles of potassium intake had unadjusted HRs of incident DM of 1.37 (95% CI, 1.18-1.58), 1.19 (95% CI, 1.02-1.38), and 0.95 (95% CI, 0.81-1.11), respectively, compared with those in the highest quartile of potassium intake.

We conducted multivariate analyses of baseline dietary potassium intake and risk of incident DM during the 9 years of follow-up using Cox proportional hazard regression models. The covariates considered in these models were similar to the models with serum potassium as the main exposure and included the following potential confounders: age; sex; race; BMI; waist circumference; center; parental history of DM; dietary magnesium intake per total kilocalories consumed in a day; dietary calcium intake per total kilocalories consumed in a day; serum creatinine level; hypertension; systolic blood pressure (the mean of the sec-

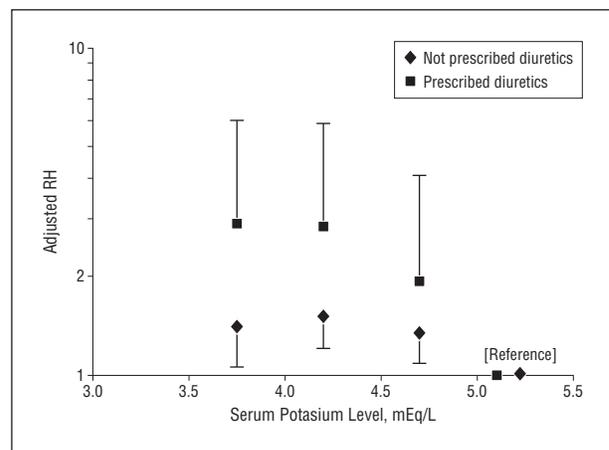


Figure 2. Adjusted relative hazard ratios (HRs) of incident diabetes mellitus (DM) by potassium category for participants prescribed diuretics and those not prescribed diuretics. Relative HRs are adjusted for age; sex; race; center; body mass index; waist circumference; serum magnesium, calcium, and creatinine levels; physical activity level; parental history of DM; presence of hypertension; systolic blood pressure (the mean of the second and third measurements); fasting glucose and fasting insulin levels; income; and use of β -blockers and angiotensin-converting enzyme inhibitors. The error bars indicate 95% confidence intervals. Results are plotted at the medians of the categories (3.8, 4.2, 4.7, and 5.2 mEq/L). To convert potassium to millimoles per liter, multiply by 1.0.

ond and third measurements); physical activity; income; and use of β -blockers, diuretics, and ACEIs. In a no-interaction, multivariate model, there was no significant association between dietary potassium intake and DM risk. When compared with those in the highest potassium intake quartile (≥ 1.93 mg/kcal), those with intakes of less than 1.37 mg/kcal, 1.37 to less than 1.63 mg/kcal, and 1.63 to less than 1.93 mg/kcal had HRs of incident DM of 1.03 (95% CI, 0.81-1.31), 1.05 (95% CI, 0.86-1.29), and 0.86 (95% CI, 0.72-1.03), respectively. When dietary potassium was used as a continuous variable or as a categorical variable alone, with a separate variable for total kilocalorie intake, there was still no significant association with risk of incident DM.

We did, however, observe a significant interaction between dietary potassium intake and income in the mul-

tivariate model ($P = .01$). Among those participants in the lowest income group (<\$12 000 annual family income in 1986 US dollars), there was a similar increase in risk of developing DM with lower dietary potassium intake. When compared with those in the highest potassium intake quartile (≥ 1.93 mg/kcal), those with intakes of less than 1.37 mg/kcal, 1.37 to less than 1.63 mg/kcal, and 1.63 to less than 1.93 mg/kcal had HRs of incident DM of 1.81 (95% CI, 1.04-3.14), 1.70 (95% CI, 1.06-2.74), and 0.83 (95% CI, 0.52-1.31), respectively. A significant increase in risk of DM was not found among those participants in higher income groups. In contrast, there was no significant interaction between dietary potassium intake and either age, sex, race, or BMI ($P > .05$ for all comparisons).

COMMENT

Our study suggests an inverse relationship between serum potassium levels and risk of incident DM in middle-aged adults. This relationship was independent of a wide array of potentially confounding factors, was stronger in thiazide users but present in their non-thiazide-using counterparts, was still detectable more than 17 years later, and was robust in a variety of sensitivity analyses. In contrast, we did not find such a robust association between dietary potassium intake and incident DM after taking into account effect modification and adjusting for potential confounders.

Since the 1980s, several small-scale epidemiological studies of the effects of antihypertensive agents on the risk of DM have been conducted, many of which suggested an increased risk of DM with the use of thiazide diuretics; however, many of these studies were not optimal owing to sample size or study design.¹² Since 2000, a few large-scale epidemiologic studies¹²⁻¹⁴ have been conducted, assessing the association of thiazide diuretic use and glucose metabolism, and have found inconsistent relationships. Analysis of data from the Nurses' Health Studies I and II and Health Professionals Follow-up Study did find an increased risk of DM associated with diuretic use,¹⁴ whereas analysis of data from the ARIC Study¹² and the United Kingdom's General Practice Research Database¹³ did not find an independent association between thiazide diuretic use alone and increased risk of DM. Analyses of data from clinical trials have focused on thiazide-induced hypokalemia. A review of data from 59 clinical trials, which had arms in which participants were prescribed thiazide diuretics, found a significant inverse correlation between glucose and potassium levels and found that potassium supplementation was associated with smaller increases in glucose levels.¹ A recent analysis of the SHEP trial found that low potassium level was the primary mediator of the association between thiazide diuretics and increased risk of DM.⁵ None of the epidemiologic studies or clinical trials in our review of the literature has looked at the association of potassium levels, independent of diuretic use, and risk of DM, which was the aim of our study.

Strengths of this study include the population-based sampling method of ARIC, a biracial cohort, availability

of blood measurements, extensive data on potential confounders, a large sample size that increased precision and permitted simultaneous statistical adjustment for multiple variables, and long duration of follow-up that offered the opportunity to study long-term risk. In addition, the number of participants prescribed medications at the baseline visit that could have affected serum potassium levels was relatively small, allowing for a fairly robust analysis of serum potassium levels unaffected by medications.

Nonetheless, several limitations of our study deserve mention. First, our main exposure, serum potassium, was based on a single measurement at the baseline visit and is subject to intra-individual variability. However, the short-term intra-individual variability of potassium has been assessed in the ARIC Study and the National Health and Nutrition Examination Survey (NHANES) III. Both studies found serum potassium levels to have an intra-individual variability of approximately 5%, based on repeated measurements taken approximately 2 weeks apart, which is relatively low compared with other measures.^{15,16} Accounting for this variability would likely strengthen the association found between serum potassium level and the risk of incident DM. Improper specimen handling would usually result in increased serum potassium (eg, from hemolysis), which would also bias results toward the null. Hence, our findings are robust to this potential bias. One measure of fasting insulin level, which we used in our model, is not a reliable measure of insulin levels or degree of insulin resistance. To help account for this unreliable measure, we included 2 measures of obesity, BMI and waist circumference, which could potentially better reflect the degree of insulin resistance. The method of DM ascertainment differed in the in-person visit data and the telephone follow-up data. Based on other studies, both methods are valid for a diagnosis of DM¹⁷ but may differ somewhat in their rate of case ascertainment.

An observational study cannot prove causality. It is possible that serum potassium could exert its effect on DM risk through other pathways and may not have a direct impact on DM risk. However, earlier studies using techniques including hyperglycemic clamps and experimentally induced hypokalemia do suggest a direct and causal relationship with the induction of defects of insulin secretion by hypokalemia.^{2,3,18} While a direct relationship between serum potassium and glucose metabolism is possible, as evidenced by these studies, other potential mediators of this relationship, such as aldosterone, should be considered. Measures of aldosterone and other hormones of the renin-angiotensin-aldosterone system, which directly affect serum potassium levels and could possibly affect glucose metabolism, were not available in this cohort.

Assessing a causal relationship between dietary potassium intake and DM is more difficult. First, accurate measurement of dietary potassium intake is difficult by questionnaires. The reliability of dietary potassium measurement is likely to be less than that of serum potassium, and measurement error could have affected the relationship seen between dietary measures as exposures and our outcome of interest. The reliability of dietary po-

tassium has not been assessed in the ARIC Study; however, estimates are reasonable and comparable with national estimates.¹⁹ Also, dietary potassium could be a marker of other substances in the diet that are contained in the same foods that are high in potassium and that could exert an effect on DM risk. One study looked at the relationship between risk of DM and dietary potassium in the Nurses' Health Study cohort. This study found an association between low potassium intake and increased risk of DM but controlled for only 2 other dietary factors, dietary magnesium and dietary calcium, in the model.²⁰ Other related factors could be mediators in this relationship. The interaction seen between dietary potassium and income also deserves further investigation because other risk factors, including other dietary factors or lifestyle behaviors that could be associated with low income, could be mediating the higher risk of DM seen in this group of participants.

The findings of this study deserve further investigation. The association between increased risk of DM and low serum potassium levels seen in this cohort should be assessed in other populations. Finally, clinical trials should be developed to assess if increasing serum potassium, through medications, pharmacologic supplementation, or increased dietary intake—all relatively simple interventions—could indeed reduce the risk of incident DM.

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