ABSTRACT

Background: Low serum potassium appears to be independently associated with incident type 2 diabetes, and low dietary potassium is more common in African Americans than in whites.

Objective: We hypothesized that low serum potassium contributes to the excess risk of diabetes in African Americans.

Design: We analyzed data collected from 1987 to 1996 from the Atherosclerosis Risk in Communities (ARIC) Study. At baseline, we identified 2716 African American and 9493 white participants without diabetes. We used multivariate Cox models to estimate the relative hazards (RHs) of incident diabetes related to baseline serum potassium during 9 y of follow-up.

Results: Mean serum potassium concentrations were lower in African Americans than in whites at baseline (4.2 compared with 4.5 mEq/L; \( P < 0.01 \)), and African Americans had a greater incidence of diabetes than did whites (26 compared with 13 cases/1000 person-years). The adjusted RHs (95% CI) for incident diabetes for those with serum potassium concentrations of <4.0, 4.0–4.4, and 4.5–4.9 mEq/L, compared with those with serum potassium concentrations of 5.0–5.5 mEq/L (referent), were 2.28 (1.21, 4.28), 1.97 (1.06, 3.65), and 1.85 (0.99, 3.47) for African Americans and 1.53 (1.14, 2.05), 1.49 (1.19, 1.87), and 1.27 (1.02, 1.58) for whites, respectively. Racial differences in serum potassium appeared to explain 18% of the excess risk of diabetes in African Americans, which is comparable with the percentage of risk explained by racial differences in body mass index (22%).

Conclusions: Low serum potassium concentrations in African Americans may contribute to their excess risk of type 2 diabetes relative to whites. Whether interventions to increase serum potassium concentrations in African Americans might reduce their excess risk deserves further study. The ARIC Study is registered at clinicaltrials.gov as NCT00005131. Am J Clin Nutr doi: 10.3945/ajcn.110.007286.

INTRODUCTION

Diabetes mellitus imposes a substantial burden on the public health of the United States, affecting >8% of Americans and costing >$174 billion in 2007 (1). This burden falls disproportionately on African Americans. Recent estimates from the National Health and Nutrition Examination Survey (NHANES) 2005–2006 found that the adjusted prevalence of diabetes among African Americans is 70% higher than that for non-Hispanic whites (2). Many factors are thought to contribute to the greater prevalence of diabetes in African Americans, including differences in socioeconomic status, diet, health behaviors, obesity, and genetic predisposition (3, 4). However, the racial disparity in diabetes risk is not fully explained by differences in traditional risk factors, and other novel factors likely contribute to this increased risk.

Serum potassium is a novel risk factor for diabetes that could potentially explain some of the racial disparity in diabetes risk. Serum potassium predicts the development of several medical conditions, including hypertension and glucose intolerance (5, 6). Compared with their white counterparts, African Americans have been found to consume less potassium in their diet, to excrete less potassium in their urine, and to display a greater blood pressure–lowering response to potassium supplementation (6–9).

Serum potassium and diabetes have been linked primarily in studies related to the use of thiazide diuretics. Low serum potassium partially mediates the relation between the use of thiazide diuretics and the increased risk of diabetes (10, 11). Studies have also suggested that higher potassium concentrations may help confer the protective effects that have been found from agents blocking the renin-tensin-aldosterone system by decreasing risk of diabetes (12). In a previous study, we found a significant inverse relation between serum potassium and diabetes risk independent of diuretic use (13). We therefore hypothesized that

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2 Portions of this work were presented orally at the National Heart, Lung, and Blood Institute’s Cardiovascular, Epidemiology, Biostatistics, and Prevention Trainee Session, San Francisco, CA, March 2010, and as a poster at the American Heart Association Conference on Cardiovascular Disease Epidemiology, San Francisco, CA, March 2010.
3 The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by the National Heart, Lung, and Blood Institute (contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022). H-CY and FLB were supported by a Diabetes Research and Training Center Grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (P60 DK079637). FLB was supported by a grant from the National Institutes of Health, NIDDK, Bethesda, MD (K24 DK62222).
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racial differences in serum potassium would partially account for the excess risk of incident diabetes in African Americans.

SUBJECTS AND METHODS

To test our hypothesis, we analyzed data from the Atherosclerosis Risk in Communities (ARIC) Study, a prospective cohort study of 15,792 adults between the ages of 45 and 64 y of age at baseline. The participants were recruited from 4 US communities. They attended an initial baseline visit between 1987 and 1989, with recruitment beginning at the 4 sites in 1987. Three subsequent visits took place every 3 y for 9 y of follow-up. Details of the design and conduct of the ARIC Study were published previously (14). Institutional review boards at each of the participating institutions approved the study, and informed consent was obtained from each participant.

Exclusions

We excluded participants sequentially from this analysis if, at the baseline visit, they had diabetes (n = 1870), defined as 1) a fasting glucose concentration ≥ 126 mg/dL, 2) a nonfasting glucose concentration of ≥ 200 mg/dL, 3) participant report of a physician diagnosis, or 4) use of medications to treat diabetes (15). We further excluded participants with missing baseline diabetes information or missing serum potassium concentrations (n = 148), a high serum potassium concentration (>5.5 mEq/L; n = 156), ethnicity other than African American or white (n = 44), fasting <8 h (n = 257), a serum creatinine concentration >1.7 mg/dL (n = 75), or missing information on incident diabetes or other relevant covariates (n = 1033). Our final study sample consisted of 12,209 (2716 African American and 9493 white) participants who had complete data and were initially free of diabetes.

Incident type 2 diabetes

The main outcome was incident diabetes, defined as above (15). For this definition, the date of onset of diabetes was estimated by linear interpolation by using fasting glucose values at the visit at which diabetes was ascertained and the immediately preceding visit (15).

Exposures

The main exposure of interest in certain analyses was serum potassium. Blood samples were collected and then processed in a standardized fashion: samples were partitioned into aliquots, centrifuged, frozen, and stored at −70°C in a central laboratory (14). Serum potassium concentrations, from both the baseline visit and the second visit, which was conducted 3 y after the baseline visit, were measured with a direct electrochemical technique on undiluted serum (16). The main exposure in our assessment of mediation was self-reported race: African American or white.

Covariates

Potential covariates thought to affect the relation between serum potassium and incident diabetes or the relation between race and incident diabetes included different demographic variables, anthropometric values, and laboratory values. We included the following covariates in our models: age, sex, center, BMI, leisure-time physical activity level, parental history of diabetes, presence of hypertension, average of systolic blood pressure readings from the second and third measurements, fasting glucose, fasting insulin, combined family income, education, use of β-blockers, use of diuretics, use of angiotensin converting enzyme (ACE) inhibitors, and serum concentrations of magnesium, calcium, and creatinine. Demographic information and information on parental history, physical activity, income, education, and medication use were obtained during an in-person interview; anthropometric and laboratory measurements were obtained in a standardized fashion by trained personnel (16, 17).

Statistical analyses

We compared the means and SDs or frequency of baseline characteristics of the study population by race using Student’s t tests for continuous variables and Pearson’s chi-square tests for categorical variables. We used Cox proportional hazard regression models, stratified by race, to investigate the association between baseline serum potassium concentrations and incident diabetes after adjustment for potential confounding variables, which were chosen a priori. Potassium was handled as 1) a continuous variable, 2) a categorical variables based on clinically meaningful cutoffs (<4.0, 4.0–4.4, 4.5–4.9, and 5.0–5.5 mEq/L), or 3) categorical variables based on quintiles. In categorical analyses, we used the group with the highest serum potassium concentration for reference. In sensitivity analyses, the average serum potassium value from the baseline and second visits, the only visits at which serum potassium was measured, was used as the main exposure.

We calculated the mediation effect of covariates on the association between race and risk of incident diabetes if the covariate met the following 2 criteria for being a potential mediator: 1) race was associated with the covariate and 2) the covariate predicted risk of incident diabetes controlling for race. We determined that a variable that met these 2 criteria was a “statistically significant mediator” if the addition of this variable to the model both attenuated the coefficient of race and had a statistically significant mediation effect. We calculated the mediation effect of a covariate as the percentage change in the coefficient of race in models with and without the covariate of interest. The 95% CIs were calculated by using boot-strapping with replacement (1000 samples) (18). Tests of significance were 2-tailed, with an α level of 0.05. All statistical analyses were conducted by using SAS 9.1.3 (SAS Institute, Cary, NC) and STATA/SE 10.1 (StataCorp, College Station, TX).

RESULTS

Significant differences were observed for all covariates considered in the main analyses between African Americans and whites, except for baseline fasting glucose concentrations, use of β-blockers, and use of ACE inhibitors. African Americans had a higher mean BMI, lower physical activity levels, and higher fasting insulin concentrations. They also had a greater prevalence of hypertension and parental history of diabetes and lower annual incomes and education levels than did whites. Mean serum potassium concentrations were significantly lower in African Americans than in whites (4.2 compared with 4.5 mEq/L; P < 0.01). The baseline characteristics of participants by race are
summarized in Table 1. The distribution of serum potassium by race is shown in Figure 1.

Of 2716 African Americans, 491 developed diabetes; of 9493 whites, 984 developed diabetes during 9 y of follow-up corresponding to a crude incidence rate that was twice as high in African Americans (26 compared with 13 per 1000 person-years; \( P < 0.01 \)). The relative hazard (RH) (95% CI) of incident diabetes in African Americans compared with whites was 2.11 (1.87, 2.37), adjusted for age, sex, and center (Table 2).

There was a graded inverse relation between serum potassium and incident diabetes in both African Americans and whites. In multivariate analyses stratified by race, African Americans appeared to have a higher RH (95% CI) of incident diabetes for each category of serum potassium <5.0 mEq/L compared with whites (Figure 2: Table 2). The adjusted RHs (95% CIs) of incident diabetes for those with serum potassium concentration of <4.0, 4.0–4.4, and 4.5–4.9 mEq/L, compared with those with a serum potassium concentration of 5.0–5.5 mEq/L (referent), were 2.28 (1.21, 4.28), 1.97 (1.06, 3.65), and 1.85 (0.99, 3.47) for African Americans and 1.53 (1.14, 2.05), 1.49 (1.19, 1.87), and 1.27 (1.02, 1.58) for whites, respectively. However, the serum potassium-race interaction was not statistically significant. Similar graded results were obtained when potassium was categorized into quintiles.

In the multivariate model, after further adjustment for serum potassium, age, sex, center, BMI, physical activity, parental history of diabetes, hypertension, systolic blood pressure, fasting serum glucose and insulin, combined family income, education, use of \( \beta \)-blockers, use of diuretics, use of ACE inhibitors, and serum magnesium, calcium, and creatinine concentrations, the RH (95% CI) of diabetes in African Americans compared with whites, decreased from 2.11 (1.87, 2.37) to 1.28 (1.11, 1.49), a decrease of 75% from the RH in the partially adjusted model (Table 2).

Most of the variables in our main model met the first 2 criteria as possible mediators of the association between race and risk of incident diabetes. Only the variables age, fasting glucose, and use of \( \beta \)-blockers did not meet these criteria. We found, however, that only BMI, serum potassium, and systolic blood pressure were statistically significant mediators of the association between race and risk of incident diabetes, which explained a significant fraction of the increased risk of incident diabetes in African Americans. In the multivariate model, the mediation effects were the greatest for BMI and serum potassium, with percentage mediation effects (95% CI) of 22.4% (10.0%, 48.1%) and 18.0% (7.1%, 46.6%) respectively, whereas systolic blood pressure had a much lower mediation effect (95% CI) of 5.3% (1.2%, 20.9%). The addition of serum potassium to an otherwise fully adjusted model decreased the RH (95% CI) of diabetes in African Americans compared with whites from 1.36 (1.17, 1.57) to 1.28 (1.11, 1.49) (Table 2). Fasting insulin met the first 2 criteria for being a potential mediator; however, it did not attenuate the coefficient of race when included in the model. Rather the addition of insulin to the model increased it, and this change was not statistically significant.

In analyses using the average serum potassium from the baseline and second visits as the main exposure, the average serum potassium variable continued to be significantly associated with diabetes risk (\( P = 0.0003 \)) and was still more strongly associated with diabetes in African Americans than in whites. The percentage mediation effect (95% CI) of the average serum potassium variable on the association between race and risk of incident diabetes was 17.3% (7.9%, 42.2%).

### Table 1

Baseline characteristics of 12,209 initially nondiabetic middle-aged adults by race: the Atherosclerosis Risk in Communities (ARIC) Study

|                        | African Americans (n = 2716) | Whites (n = 9493) | \( P \) value
|------------------------|-----------------------------|-------------------|----------------
| Age (y)                | 53 ± 5.7 \(^1\)            | 54 ± 5.7          | <0.01
| Female sex (%)         | 62.9                        | 53.8              | <0.01
| BMI (kg/m²)            | 29.1 ± 5.98                | 26.7 ± 4.59       | <0.01
| Parental history (%)   | 24.5                        | 22.1              | 0.01
| Hypertension (%)       | 50.6                        | 24.5              | <0.01
| Serum potassium (mEq/L)| 4.18 ± 0.45                 | 4.49 ± 0.43       | <0.01
| Serum calcium (mg/dL)  | 9.82 ± 0.46                 | 9.76 ± 0.41       | <0.01
| Serum magnesium (mEq/L)| 1.60 ± 0.16                 | 1.66 ± 0.14       | <0.01
| Serum creatinine (mg/dL)| 1.11 ± 0.20                | 1.08 ± 0.17       | <0.01
| Serum glucose (mg/dL)  | 98.7 ± 10.06                | 98.6 ± 9.01       | 0.66
| Serum insulin (pmol/L) | 95.4 ± 70.31                | 72.3 ± 52.97      | <0.01
| Physical activity \(^2\)| 2.1 ± 0.58                   | 2.5 ± 0.53        | <0.01
| Systolic blood pressure (mm Hg) | 127 ± 20 | 118 ± 17 | <0.01
| \( \beta \)-Blocker use (%) | 9.0                      | 9.4               | 0.53
| Diuretic use (%)       | 23.0                        | 12.8              | <0.01
| ACE-inhibitor use (%)  | 2.4                         | 2.5               | 0.59
| Combined family income (%) | >$50,000     | 7.7               | 0.39
|                        | $25,000–$49,999             | 21.8              | <0.01
|                        | $12,000–$24,999             | 27.6              | 18.0
|                        | <$12,000–$11,999            | 42.9              | 9.7
|                        | Education ≤ 12 y (%)        | 37.2              | 15.6 | <0.01

\(^1\) ACE, angiotensin converting enzyme.

\(^2\) Mean ± SD (all such values).

\( \beta \)-blockers, use of diuretics, use of ACE inhibitors, and serum magnesium, calcium, and creatinine concentrations, the RH (95% CI) of diabetes in African Americans compared with whites, decreased from 2.11 (1.87, 2.37) to 1.28 (1.11, 1.49), a decrease of 75% from the RH in the partially adjusted model (Table 2).

**FIGURE 1.** Distribution of serum potassium by race in 12,209 initially nondiabetic middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. Smoothed normal curves of serum potassium by race are superimposed on the histograms. Dark gray bars and solid line represent the percentage distribution of serum potassium in African Americans. White bars and dashed line represent the percentage distribution of serum potassium in whites. Mean serum potassium values differ significantly between African Americans and whites, \( P < 0.01 \) (Student’s \( t \) test).
the second and third measurements, fasting glucose, fasting insulin, combined sex, center, BMI, physical activity level, parental history of diabetes, was not significant. Cox proportional hazard models were adjusted for age, for whites, respectively. The interaction term for serum potassium and race Americans and 1.53 (1.14, 2.05), 1.49 (1.19, 1.87), and 1.27 (1.02, 1.58) 2.28 (1.21, 4.28), 1.97 (1.06, 3.65), and 1.85 (0.99, 3.47) for African with a serum potassium concentration of 5.0–5.5 mEq/L (referent), were

| TABLE 2 |
| Incidence rates and partially and fully adjusted relative hazards (RHs) for incident diabetes by race |
|           | African Americans | Whites |
| No. of incident cases of diabetes | 491 | 984 |
| Incidence of diabetes (rate/1000 person-years) | 26.28 | 13.32 |
| RH adjusted for age, sex, race, and center (95% CI) | 2.11 (1.87, 2.37) | 1.00 (ref) |
| RH adjusted for age, sex, race, center, and serum potassium (95% CI) | 1.89 (1.68, 2.14) | 1.00 (ref) |
| Fully adjusted RH, except for potassium (95% CI) | 1.36 (1.17, 1.57) | 1.00 (ref) |
| Fully adjusted RH (95% CI) | 1.28 (1.11, 1.49) | 1.00 (ref) |

1 Cox proportional hazard regression models were used to calculate RHs. ref, referent. 2 Adjusted for age, sex, center, BMI, physical activity level, parental history of diabetes, presence of hypertension, average of systolic blood pressure readings from the second and third measurements, fasting glucose, fasting insulin, combined family income, education, use of β-blockers, use of diuretics, use of angiotensin converting enzyme inhibitors, and serum concentrations of potassium, magnesium, calcium, and creatinine.

DISCUSSION

African Americans have a greater risk of developing diabetes than do whites. In the ARIC Study, African Americans had a greater prevalence of several risk factors that could potentially contribute to this disparity, including higher BMI, greater prevalence of family history of diabetes, greater prevalence of hypertension, and higher fasting insulin concentrations. African Americans also had significantly lower serum potassium concentrations than did whites. In our analysis, only BMI and serum potassium seemed to be significant mediators of the association between race and risk of incident diabetes, whereas the other traditional risk factors, individually, did not explain any significant portion of the disparity.

Studies have tried to ascertain the causative factors leading to the greater incidence of diabetes in African Americans than in whites. A previous ARIC study found that traditional risk factors accounted for ~50% of this increased risk, with adiposity as the main explanatory factor (16). A more recent study followed trends in obesity and diabetes prevalence by racial groups. This study found that, from 1971 through 2004, the racial disparity in diabetes prevalence has widened the most in normal-weight and overweight persons rather than in those with severe obesity, which suggests that additional factors other than weight contribute to this racial disparity in risk (19). Other studies have found that African Americans and whites who live in the same community have a similar risk of diabetes, which suggests that social and environmental factors, such as diet, could play a predominant role in the racial disparity in diabetes risk that is found in national surveys and studies (3, 20). However, the identity of such factors is uncertain.

Several studies have shown racial differences in potassium handling. Compared with their white counterparts, African Americans appear to have higher peak total body potassium concentrations at ~30 y of age and then show a faster rate of decline with aging (21). Studies have found that urinary excretion of potassium, which correlates strongly with dietary intake, differed and was lower in African Americans despite similar dietary potassium intakes (8, 22–25). Other studies have found that a lower intake of potassium is more strongly associated with elevated blood pressure in African Americans and that potassium supplementation has greater blood pressure–lowering effects in African Americans than in whites (6, 7, 9, 26). The mechanisms for these racial differences are unclear.

Regarding the effects of potassium on glucose metabolism, we are aware of no other studies that have looked at the differential effects of serum potassium on diabetes risk by race. However, studies have looked at the biological mechanism by which hypokalemia may lead to impaired glucose tolerance. Glucose clamp studies have shown that hypokalemia, when experimentally induced with high doses of thiazide diuretics, led to impaired insulin secretion and impaired glucose tolerance in healthy individuals (27, 28). This impaired glucose tolerance was prevented in one such study when potassium supplements were provided to prevent hypokalemia (28).

The strengths of this study include the population-based sampling method of ARIC, the biracial nature of the cohort, the availability of blood measurements, the extensive data on potential confounders, a large sample size that increased precision and permitted simultaneous statistical adjustment for multiple variables, and the long duration of follow-up that offered the opportunity to study long-term risk.

Nonetheless, several limitations of the study deserve mention. In our main analyses, we used serum potassium measurements
from the baseline visit, which are subject to measurement error. However, intradividual variability in serum potassium has been calculated in the short-term and found to be relatively small (29).

We did look at an average serum potassium value from 2 visits that were 3 y apart. This average serum potassium value continued to be significantly associated with diabetes risk, with continued racial variation in its strength of association with diabetes risk. Another limitation was that African Americans and whites in the ARIC Study were not necessarily representative of all African Americans and whites, and findings from this study may not be generalizable. Also, our outcome of incident diabetes was based on self-report and fasting blood glucose concentrations only; however, this method of diabetes case-ascertainment has been used extensively in other epidemiologic studies and has been found to be a valid method (30). Another limitation of this study was that we may not have accounted for other measurable mediators of the association between race and risk of incident diabetes.

Finally, although we did find a significant association between potassium and risk of diabetes, there may be other factors through which this association is mediated. Serum potassium is tightly regulated, and concentrations are determined by potassium intake, potassium excretion (primarily in the urine), and by factors that affect potassium excretion and partitioning between intracellular and extracellular spaces. The primary determinants of renal excretion of potassium include sodium delivery to the distal nephron and urine flow, the renin-angiotensin-aldosterone system, vasopressin concentrations, and acid-base status (31). Other hormones and chemicals affect the partitioning of potassium, such as insulin, catecholamines, thyroid hormone, and acid-base status (31). Whereas we tried to adjust for measures of some of these determinants, we did not have measurements on many of these factors.

We found that low normal serum potassium is associated with a greater risk of incident diabetes and with greater relative risks in African Americans than in whites. These findings should be verified in other populations, and clinical trials should be developed to determine whether potassium supplementation, either through diet or pharmacologic supplements, can indeed reduce the risk of diabetes and reduce the racial disparity in diabetes risk.

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REFERENCES