Changes in Serum Potassium Mediate Thiazide-Induced Diabetes

Tariq Shafi, Lawrence J. Appel, Edgar R. Miller, III, Michael J. Klag, Rulan S. Parekh

Abstract—Thiazides, recommended as first-line antihypertensive therapy, are associated with an increased risk of diabetes. Thiazides also lower serum potassium. To determine whether thiazide-induced diabetes is mediated by changes in potassium, we analyzed data from 3790 nondiabetic participants in the Systolic Hypertension in Elderly Program, a randomized clinical trial of isolated systolic hypertension in individuals aged ≥60 years treated with chlorthalidone or placebo. Incident diabetes was defined by self-report, antidiabetic medication use, fasting glucose ≥126 mg/dL, or random glucose ≥200 mg/dL. The mediating variable was change in serum potassium during year 1. Of the 459 incident cases of diabetes during follow-up, 42% occurred during year 1. In year 1, the unadjusted incidence rates of diabetes per 100 person-years were 6.1 and 3.0 in the chlorthalidone and placebo groups, respectively. In year 1, the adjusted diabetes risk (hazard ratio) with chlorthalidone was 2.07 (95% CI: 1.51 to 2.83; P<0.001). After adjustment for change in serum potassium, the risk was significantly reduced (hazard ratio: 1.54; 95% CI: 1.09 to 2.17; P=0.01); the extent of risk attenuation (41%; 95% CI: 34% to 49%) was consistent with a mediating effect. Each 0.5-mEq/L decrease in serum potassium was independently associated with a 45% higher adjusted diabetes risk (95% CI: 24% to 70%; P<0.001). After year 1, chlorthalidone use was not associated with increased diabetes risk. In conclusion, thiazide-induced diabetes occurs early after initiating treatment and appears to be mediated by changes in serum potassium. Potassium supplementation might prevent thiazide-induced diabetes. This hypothesis can and should be tested in a randomized trial. (Hypertension. 2008;52:1-8.)

Key Words: hypertension ● diabetes mellitus ● thiazide diuretics ● chlorthalidone ● hypokalemia ● potassium

Hypertension affects >65 million US adults and ≈1 billion people worldwide. It is the leading risk factor for coronary heart disease, stroke, and kidney failure. Thiazide diuretics are currently recommended as the first-line therapy of hypertension. Thiazides, however, are associated with an increased risk of developing diabetes. In the Systolic Hypertension in the Elderly Program (SHEP), use of the thiazide diuretic chlorthalidone was associated with a 50% higher risk of incident diabetes compared with placebo. Similarly, in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), treatment with chlorthalidone was associated with a 39% increased risk of incident diabetes compared withamlodipine and 48% higher risk compared with lisinopril. Continued concern regarding this increased risk of diabetes is one of the primary factors limiting the widespread use of thiazide diuretics despite the national recommendations from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

Thiazide use increases urinary potassium losses and lowers the serum potassium level. Because 98% of the total body potassium is intracellular, and serum potassium concentration is tightly regulated, frank hypokalemia (a serum potassium <3.5 mEq/L) only occurs in the setting of severe potassium depletion. A few small studies, with <50 participants observed for 1 to 4 weeks, have evaluated the effect of experimentally induced hypokalemia on glucose homeostasis. In these studies, hypokalemia was associated with hyperglycemia because of decreased insulin secretion. With moderate potassium losses, serum potassium can decrease from baseline but stay above the clinically defined threshold of hypokalemia. Furthermore, even moderate potassium loss is associated with adverse outcomes, such as increased blood pressure (BP), increased salt sensitivity, increased bone turnover, and stroke. It has been hypothesized that thiazide-induced diabetes may result from thiazide-induced changes in potassium.
The objective of this study was to determine whether thiazide-induced changes in serum potassium mediate the effect of thiazide diuretics on incident diabetes in hypertensive individuals participating in a large, randomized trial.

Methods

Design and Participants

The protocol for this analysis of the SHEP deidentified data set was approved by the Johns Hopkins Medicine Institutional Review Board. Rationale and design of the SHEP trial have been described previously. Briefly, SHEP was a randomized, multicenter, double-masked, placebo-controlled trial conducted at community-based clinics with recruitment from 1985 to 1988 and follow-up ending in 1991. The primary aim of the SHEP trial was to determine whether antihypertensive treatment reduced the risk of stroke in individuals aged ≥60 years with isolated systolic hypertension defined as systolic BP >160 mm Hg and diastolic BP <90 mm Hg.

The present analysis includes 3790 (80%) of the 4736 SHEP participants. Participants were excluded if they had baseline diabetes (n = 686 [14.5%]), no follow-up glucose (n = 164 [3.5%]), or no follow-up serum potassium (n = 96 [2%]). Baseline diabetes mellitus was defined by self-report, treatment with antidiabetic agents, fasting glucose ≥126 mg/dL, or random glucose ≥200 mg/dL.

Interventions

The participants were randomly assigned to active therapy or matched placebo. Systolic BP goal was defined as a reduction of 20 mm Hg if systolic BP was between 160 and 179 mm Hg and reduction to systolic BP <160 mm Hg for those with higher BP. Participants were started on either chlorthalidone 12.5 mg daily or matched placebo. Drug dosage (or matched placebo) was doubled if the BP remained above goal at 8 weeks. If the BP remained above goal at 16 weeks despite the doubling of dose, atenolol or reserpine (or matched placebo) was added to the regimen.

Pertinent Laboratory Measurements

Serum potassium was measured at baseline, within a month of initiating and/or increasing the dose of chlorthalidone (or matched placebo) and then annually. Serum potassium was also measured again in follow-up of abnormal values. Potassium supplementation was prescribed if serum potassium was <3.5 mEq/L at 2 consecutive visits. Fasting blood samples were obtained at baseline and then at first, third, and final annual visits but were not required for study participation. Fasting glucose was measured in 2273 participants (60%) at baseline. Among 1517 participants without fasting glucose measurement, random glucose was available for 1374 (91%).

Exposure, Outcome, and Mediating Variables

The primary exposure for this analysis was treatment with chlorthalidone. The primary outcome was incident diabetes defined by self-report, treatment with antidiabetic agents, fasting glucose ≥126 mg/dL, random glucose ≥200 mg/dL, or diabetes noted on hospitalization records. The mediating variable was change in serum potassium during year 1, because we expected most decline in serum potassium to occur early after initiating chlorthalidone. Change in potassium during year 1 was adjusted for baseline potassium to reduce the effect of regression to the mean. Sensitivity analyses were conducted in which the mediating variable, mean potassium in year 1, was replaced with either the highest potassium in year 1 or serum potassium as a time-dependant covariate.

Other Covariates

Other covariates in the model included baseline values for the following: age, gender, race (nonwhite versus white), body mass index (BMI, weight [kilograms]/height^2 [meters]), systolic and diastolic BPs, serum creatinine, fasting serum glucose, and serum potassium. Missing data for baseline variables were as follows: BMI 1.3%, diastolic BP 0.2%, serum glucose 3.6%, serum potassium 4.8%, and serum creatinine 5.0%. Baseline potassium was more likely to be missing from the placebo group than from the chlorthalidone group (5.6% versus 4.0%; P = 0.02). There were no other differences in missing variables between the 2 groups.

Analytic Methods

Continuous variables were compared using t tests for parametric data and rank-sum test or robust regression for nonparametric data. Categorical variables were compared using the χ^2 test. Missing baseline data values were imputed with 10 data replicates using ice and micompute programs in Stata (Stata Corp). Participants free of diabetes were censored at death, at the end of the trial, or at the last annual visit date for those lost to follow-up. Cumulative incidence of diabetes was assessed using the nonparametric Kaplan-Meier product-limit estimator. Incidence rates (IR) of diabetes were calculated using the person-time approach. Linear association between the independent continuous variables and diabetes was assessed visually using lowess smoothed log-odds plots. In the final model, BMI was analyzed as a linear spline with a knot at 20 kg/m^2 and fasting glucose as a linear spline with a knot at 100 mg/dL. The association between change in serum potassium and diabetes was linear based on visual inspection of smoothed log-odds plots, and there was no improvement in model fit using splines based on quartiles and clinical cutoffs. Cox proportional hazards regression with treatment-time interaction was used to model the adjusted risk of diabetes with chlorthalidone compared to placebo. Proportional hazards assumptions were assessed graphically and by hypothesis-based tests. Number needed to harm was calculated as recommended for survival analysis. The mediating variable was defined as a predictor hypothesized to lie on the causal pathway between exposure and outcome. Mediation was assessed in the following 5 steps:

1. Determine whether the exposure (chlorthalidone) predicts the mediator (change in serum potassium); (2) determine whether the mediator (change in serum potassium) independently predicts the outcome (diabetes); (3) determine the adjusted hazard ratio (HR) of diabetes from chlorthalidone without including change in potassium in the regression model (this HR represents the “total effect” of chlorthalidone); (4) determine the adjusted HR of diabetes from chlorthalidone with change in potassium in the regression model (this HR represents the “direct effect” of chlorthalidone without the effect mediated by changes in potassium); (5) calculate mediation, which represents the change in the coefficient (log HR) of chlorthalidone after adjustment for change in potassium. Mediation was calculated as follows; (coefficient for total effect – coefficient for direct effect)/coefficient for total effect × 100. Mediation was considered significant if the log HR was attenuated by >15%. A bias-corrected 95% CI for mediation was calculated using bootstrapping with replacement (1000 samples).

The probability of incident diabetes in year 1 by treatment assignment and change in potassium was predicted using the adjusted Cox regression model. A number of different sensitivity analyses were conducted to determine the robustness of our results. The risk of incident diabetes with different doses of chlorthalidone, as well as with the combination of chlorthalidone and atenolol, was determined. The effect of potassium supplementation on incident diabetes mellitus was also assessed. Data were analyzed using Stata 9.2. Statistical significance was defined as P < 0.05 using 2-tailed tests.

Results

The baseline characteristics of 3790 participants are presented in Table 1. There were no significant differences between the 2 randomized groups. There were 459 incident cases of
diabetes during 15,830 person-years of follow-up. Of the 459 cases, 266 were in the chlorthalidone group and 193 in the placebo group. The median follow-up time was 4.4 years (interquartile range: 3.5 to 5.1 years). The higher unadjusted cumulative incidence of diabetes in the chlorthalidone group (Figure 1) was apparent at year 1, when first annual fasting glucose measurements were performed. Of the 459 incident cases, 266 were in the chlorthalidone group and 193 in the placebo group. The unadjusted IR of diabetes mellitus between the 2 groups (chlorthalidone: 2.4; placebo: 2.3; P for IR ratio = 0.7).

**Figure 1.** Unadjusted cumulative incidence of diabetes in the 3790 nondiabetic participants from the SHEP trial.

**Figure 2.** Unadjusted incidence rates of diabetes in year 1 by change in serum potassium in the 3790 nondiabetic participants from the SHEP trial.

### Assessment of Change in Serum Potassium as a Mediating Variable

**Step 1: Chlorthalidone-Induced Change in Serum Potassium**

Chlorthalidone use was associated with lowering of serum potassium. During year 1, the average serum potassium (SD) was significantly lower in the chlorthalidone group (4.1 [0.4] mEq/L) than in placebo group (4.5 [0.3] mEq/L; *P*<0.001). This change represented a decrease of 0.4 (0.4) mEq/L from baseline in the chlorthalidone group during year 1 (*P*<0.001). There was no change in serum potassium in the placebo group.

**Step 2: Changes in Serum Potassium and Diabetes**

During year 1, greater decrease in serum potassium was associated with a higher unadjusted IR of diabetes (Figure 2). In the fully adjusted Cox proportional hazards model, each 0.5-mEq/L decrease in serum potassium from the average baseline level was associated with a 45% higher risk of incident diabetes (95% CI: 24% to 70% higher risk; *P*<0.001) throughout the study period. The highest risk was observed in individuals with a >0.5-mEq/L decrease in serum potassium (Table 2).

**Step 3: Chlorthalidone-Induced Diabetes (Total Effect of Chlorthalidone)**

In a Cox proportional hazards model, adjusted for age, gender, race, BMI, systolic and diastolic BP, serum creatinine, and fasting glucose (Table 3), the risk of diabetes from chlorthalidone during year 1 was 2 times higher than placebo (HR: 2.07; 95% CI: 1.51 to 2.83; *P*<0.001). The number needed to harm was 29 (95% CI: 17 to 60). After year 1, chlorthalidone was not associated with increased diabetes risk (HR: 1.08; 95% CI: 0.84 to 1.39; *P* = 0.6).

**Step 4: Chlorthalidone-Induced Diabetes (Direct Effect of Chlorthalidone)**

The Cox model for the total effect of chlorthalidone (step 3) was further adjusted for change in serum potassium. The HR for the direct effect of chlorthalidone in this model was 1.54 (95% CI: 1.09 to 2.17; number needed to harm: 57; 95% CI: 27 to 329; *P* = 0.01).

**Table 1.** Baseline Characteristics of the 3790 Nondiabetic Participants From the SHEP Trial

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo</th>
<th>Chlorthalidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomly assigned</td>
<td>1862 (49.1)</td>
<td>1928 (50.9)</td>
</tr>
<tr>
<td>Age, y</td>
<td>72 (6.6)</td>
<td>72.3 (6.7)</td>
</tr>
<tr>
<td>Gender</td>
<td>791 (42.5)</td>
<td>812 (42.1)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>1071 (57.5)</td>
<td>1116 (57.9)</td>
</tr>
<tr>
<td>White</td>
<td>1516 (81.4)</td>
<td>1550 (80.4)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>346 (18.6)</td>
<td>378 (19.6)</td>
</tr>
<tr>
<td>Baseline systolic BP, mm Hg</td>
<td>169.9 (9.2)</td>
<td>170.4 (9.9)</td>
</tr>
<tr>
<td>Baseline diastolic BP, mm Hg</td>
<td>76.6 (9.6)</td>
<td>76.7 (9.9)</td>
</tr>
<tr>
<td>Baseline BMI, kg/m²</td>
<td>27.3 (5.0)</td>
<td>27.4 (4.9)</td>
</tr>
<tr>
<td>Baseline fasting glucose, mg/dL</td>
<td>4.5 (0.5)</td>
<td>4.5 (0.5)</td>
</tr>
</tbody>
</table>

Data are N (%) or mean (SD). GFR indicates glomerular filtration rate. GFR (mL/min/1.73 m²) = 186 × (serum creatinine)/1.154 × (age) − 0.203 × (0.742 if female) × 1.210 if African American.
Table 3. Sensitivity Analyses for the Risk of Diabetes in Year 1 in the 3790 Nondiabetic Participants From the SHEP Trial

<table>
<thead>
<tr>
<th>Models</th>
<th>Change in Potassium</th>
<th>No.</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Continuous</td>
<td>3790</td>
<td>1.45 (1.24 to 1.70)</td>
<td>&lt;0.001</td>
<td>1.54 (1.09 to 2.17)</td>
<td>0.01</td>
<td>40.7 (34.3 to 49.3)</td>
</tr>
<tr>
<td></td>
<td>(per 0.5 mEq/L decrease)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>Quartile 1: ≤ −0.1*</td>
<td>806</td>
<td>Reference</td>
<td>0.001</td>
<td>1.56 (1.09 to 2.20)</td>
<td>0.01</td>
<td>36.4 (29.2 to 44.7)</td>
</tr>
<tr>
<td></td>
<td>Quartile 2: −0.1 to 0.2**</td>
<td>995</td>
<td>1.19 (0.87 to 1.62)</td>
<td>0.26</td>
<td>1.49 (1.07 to 2.08)</td>
<td>0.02</td>
<td>45.1 (39.2 to 53.5)</td>
</tr>
<tr>
<td></td>
<td>Quartile 3: 0.2 to 0.5</td>
<td>950</td>
<td>1.39 (0.99 to 1.94)</td>
<td>0.06</td>
<td>1.49 (1.07 to 2.08)</td>
<td>0.02</td>
<td>45.1 (39.2 to 53.5)</td>
</tr>
<tr>
<td></td>
<td>&gt;0.5</td>
<td>858</td>
<td>1.99 (1.35 to 2.94)</td>
<td>0.001</td>
<td>1.52 (1.07 to 2.19)</td>
<td>0.02</td>
<td>41.3 (34.4 to 51.1)</td>
</tr>
</tbody>
</table>

Change in potassium indicates baseline potassium—mean potassium during year 1 (in mEq/L). Cox regression adjusted for treatment assignment, age, gender, race, BMI, systolic and diastolic BP, baseline serum creatinine, and baseline fasting serum glucose.

*Minus sign and values <0 indicate that mean potassium in year 1 was higher than baseline potassium.

Step 5: Calculating Mediation

In the direct model for chlorthalidone-induced diabetes (step 4), there was a marked attenuation in the coefficient (log HR) of diabetes from chlorthalidone (mediation: 40.7%; 95% CI: 34.3% to 49.3%). This change exceeds the >15% attenuation criterion for mediation (Table 3).

Figure 3 graphically depicts the risk of developing diabetes based on assignment to chlorthalidone or placebo and the occurrence of 0.5-mEq/L decline in serum potassium. Treatment with chlorthalidone and/or lowering of serum potassium was associated with a higher probability of developing diabetes mellitus compared with assignment to placebo and no decrease in potassium from baseline.

Sensitivity Analyses

With restricting the analysis to participants with fasting serum glucose available at baseline and year 1 or changing the definition of incident diabetes (self-reported diagnosis, use of antidiabetic medications, or fasting serum glucose ≥140 mg/dL), the magnitude and direction of mediation were unchanged (Table 3). A 6-month lag analysis and analysis restricted to participants with baseline fasting glucose <100 mg/dL and random glucose <125 mg/dL also showed similar results, suggesting that the observed high early risk of diabetes mellitus was not because of preclinical disease. Similar results were obtained when the definition of the mediating variable (change in serum potassium) was modified. Analyses performed without

Table 3. Sensitivity Analyses for the Risk of Diabetes in Year 1 in the 3790 Nondiabetic Participants From the SHEP Trial

<table>
<thead>
<tr>
<th>Models for Diabetes Risk*</th>
<th>No. of Participants</th>
<th>Total Effect (Not Adjusted for Change in Potassium) HR (95% CI)</th>
<th>P</th>
<th>Direct Effect (Adjusted for Change in Potassium) HR (95% CI)</th>
<th>P</th>
<th>Mediation % (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td></td>
<td></td>
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<tr>
<td>Main model for the risk of diabetes*</td>
<td>3790</td>
<td>2.07 (1.50 to 2.83)</td>
<td>&lt;0.001</td>
<td>1.54 (1.09 to 2.17)</td>
<td>0.01</td>
<td>40.7 (34.3 to 49.3)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td></td>
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<tr>
<td>Available fasting glucose</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose at baseline and year 1</td>
<td>1736</td>
<td>2.05 (1.36 to 3.10)</td>
<td>0.001</td>
<td>1.63 (1.05 to 2.52)</td>
<td>0.03</td>
<td>32.0 (24.2 to 41.4)</td>
</tr>
<tr>
<td>Changing diabetes definition§</td>
<td>3888</td>
<td>1.22 (0.83 to 1.80)</td>
<td>0.32</td>
<td>0.88 (0.58 to 1.34)</td>
<td>0.56</td>
<td>164.3 (99.6 to 418.3)</td>
</tr>
<tr>
<td>≥140</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Evaluating pre-existing disease</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Six-month lag analysis‡</td>
<td>3786</td>
<td>2.09 (1.53 to 2.85)</td>
<td>&lt;0.001</td>
<td>1.57 (1.11 to 2.20)</td>
<td>0.01</td>
<td>38.8 (32.9 to 47.1)</td>
</tr>
<tr>
<td>Random glucose &lt;125 and fasting glucose &lt;100¶</td>
<td>2502</td>
<td>1.77 (1.07 to 2.92)</td>
<td>0.03</td>
<td>1.22 (0.71 to 2.09)</td>
<td>0.47</td>
<td>65.2 (50.0 to 91.3)</td>
</tr>
<tr>
<td>Different potassium measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest potassium in year 1</td>
<td>3790</td>
<td>2.07 (1.51 to 2.83)</td>
<td>&lt;0.001</td>
<td>1.49 (1.07 to 2.08)</td>
<td>0.02</td>
<td>45.1 (39.2 to 53.5)</td>
</tr>
<tr>
<td>Time-varying potassium#</td>
<td>3790</td>
<td>1.71 (1.32 to 2.22)</td>
<td>&lt;0.001</td>
<td>1.49 (1.13 to 1.96)</td>
<td>&lt;0.01</td>
<td>25.7 (10.4 to 47.1)</td>
</tr>
<tr>
<td>Without data imputation**</td>
<td>2241</td>
<td>2.39 (1.59 to 3.58)</td>
<td>&lt;0.001</td>
<td>1.88 (1.22 to 2.91)</td>
<td>&lt;0.01</td>
<td>27.5 (10.5 to 58.7)</td>
</tr>
<tr>
<td>Adjustment for BP at year 1 Annual visit††</td>
<td>3790</td>
<td>2.04 (1.45 to 2.87)</td>
<td>&lt;0.001</td>
<td>1.52 (1.07 to 2.19)</td>
<td>0.02</td>
<td>41.3 (34.4 to 51.1)</td>
</tr>
</tbody>
</table>

Change in potassium = baseline serum potassium—mean serum potassium during year 1 (in milliequivalents per liter). All of the glucose values refer to baseline serum glucose in milligrams per deciliter.

*Minus sign and values <0 indicate that mean potassium in year 1 was higher than baseline potassium.

††Model adjusted for baseline and year 1 systolic and diastolic BPs.
data imputation and analyses adjusting for attained BP at year 1 also yielded results similar to primary analysis.

Other Risk Factors for Diabetes

Nonwhite race, higher BMI, and fasting serum glucose were all independently associated with a higher risk of diabetes in year 1 (Table 4). The HR per 10-mg/dL increase in fasting glucose was 1.87 among those with baseline fasting glucose <100 mg/dL and 3.23 among those with a baseline level ≥100 mg/dL. At the time of the first annual visit, in the active therapy group 65% of the participants were taking chlorthalidone ≤12.5 mg/d, 23% were taking chlorthalidone 25 mg/d, and 12% were taking atenolol in addition to chlorthalidone. Higher doses of chlorthalidone and the use of atenolol were associated with a higher risk of diabetes in year 1. In “on-treatment analyses,” the risk of diabetes was similar to the main analysis in those deemed compliant based on urinary chlorthalidone assays. Hypokalemia (serum potassium ≤3.5 mEq/L) was noted during year 1 in 444 participants (23%) in the chlorthalidone group and 58 participants (3.1%) in the placebo group. Potassium supplement use in year 1, however, was recorded for only 7.1% and 2.9% of the participants in the chlorthalidone and placebo groups, respectively, and the mean (SD) potassium dose was 24 (12) mEq/d. These data suggest potassium supplement use, both frequency and amount, were incompletely reported. Adjustment for potassium supplement use in year 1 did not attenuate the risk of diabetes associated with change in serum potassium or chlorthalidone use. Serum potassium levels after supplementation were not available in the database.

Discussion

In our analyses of the hypertensive, nondiabetic participants in the SHEP trial, 2 principal findings emerged. First, thiazide-induced diabetes occurred early after initiating therapy. The 2-fold higher risk of diabetes from chlorthalidone was confined to the first year of the study. After year 1, chlorthalidone use was not associated with increased risk of diabetes. Second, this chlorthalidone-induced diabetes appeared to be mediated by changes in serum potassium. Each 0.5-mEq/L decrease in serum potassium from the baseline during year 1 was associated with a 45% higher risk of diabetes, independent of treatment assignment, and this effect persisted throughout the study period.

Table 4. Factors Associated With Diabetes Risk in Year 1 in the 3790 Nondiabetic Participants From the SHEP Trial

<table>
<thead>
<tr>
<th>Models for Diabetes Risk*</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: baseline characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race (Nonwhite vs white)</td>
<td>1.32 (1.06 to 1.64)</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI (per 5 kg/m²)</td>
<td>1.23 (1.12 to 1.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (per 10 mg/dL)</td>
<td>1.87 (0.99 to 3.55)</td>
<td>0.05</td>
</tr>
<tr>
<td>Fasting glucose ≥100 mg/dL</td>
<td>3.23 (2.48 to 4.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Models 2 to 4: post-randomization characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2: medication doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone (≤12.5 mg) vs placebo</td>
<td>1.70 (1.19 to 2.43)</td>
<td>0.003</td>
</tr>
<tr>
<td>Chlorthalidone (25 mg) vs placebo</td>
<td>2.37 (1.55 to 3.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chlorthalidone (25 mg) + atenolol vs placebo</td>
<td>3.16 (1.90 to 5.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P trend</td>
<td>&lt;0.001§</td>
<td></td>
</tr>
<tr>
<td>Model 3: potassium supplement use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplement use vs no use</td>
<td>0.89 (0.47 to 1.68)</td>
<td>0.7</td>
</tr>
<tr>
<td>Model 4: On treatment analysis#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone vs placebo</td>
<td>2.30 (1.5 to 3.51)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Cox regression adjusted for treatment assignment, age, gender, race, BMI, systolic and diastolic BP, baseline serum creatinine, and baseline fasting serum glucose.
†Above 20 kg/m².
§P value for interaction between potassium supplement use and change in potassium = 0.5.
Data show any reported potassium supplement use during year 1.
§P value for interaction between potassium supplement use and change in potassium = 0.03.
‡Because of study design (stepped care), atenolol was added if BP was not at goal with chlorthalidone at 25 mg/d.
#Data are for on-treatment analysis excluding drop-ins (placebo-assigned participants with negative urinary chlorthalidone assay) and drop-outs (chlorthalidone-assigned participants with positive urinary chlorthalidone assay).
decrease in total body potassium. In our analysis, greater decrease in serum potassium from baseline was associated with a higher risk of diabetes. If potassium depletion is underestimated by serum potassium, then our finding of 41% mediation may be an underestimation, and the actual degree of mediation may be much higher. We could not detect a beneficial effect of potassium supplementation on diabetes in our analysis. A likely reason for this finding is incomplete recording of potassium supplement use. Other possible reasons include a low threshold for initiating supplementation (serum potassium <3.5 mEq/L on 2 occasions) and inadequate repletion.

The association between thiazide diuretics and diabetes has been known for ~50 years. In small clinical experiments, potassium depletion induced with or without diuretics was associated with glucose intolerance, which reversed with potassium supplementation. Glucose intolerance, however, did not improve in a trial of potassium supplementation in 16 patients with 6 weeks of follow-up. A previous analysis of SHEP, using a 140-mg/dL cutoff for fasting glucose/insulin resistance for the practitioner and for future research. For the practitioner, our study suggests that trials of potassium supplementation to prevent diabetes may not need to last for 1 year to observe a difference in outcomes.

A previous analysis of SHEP, using a 140-mg/dL cutoff for fasting glucose to diagnose diabetes, had noted an increased incidence of diabetes with chlorthalidone, but the results were not statistically significant. Our analysis, using the currently accepted cutoff for fasting glucose (≥126 mg/dL), resulted in a higher number of incident diabetes cases in year 1 (n = 191) as compared with the original report from SHEP (n = 120). Sensitivity analysis using the older definition (Table 3) resulted in a statistically nonsignificant HR for diabetes in year 1, but the direction of mediation by change in serum potassium was similar to the primary analysis.

The cardiovascular risk associated with thiazide-induced diabetes continues to be a subject of ongoing debate. Some have suggested that this diabetes is different from "naturally occurring" diabetes, whereas others have argued that this "new-onset diabetes" is not benign. The increased risk of diabetes with chlorthalidone during year 1 noted in our study was based mostly on detecting changes in fasting serum glucose. This initial increased risk, followed by no risk of diabetes mellitus for the remainder of the trial duration, suggests a potential biochemical "unmasking" of diabetes in those individuals at higher risk of diabetes at baseline.

Pancreatic release of insulin is controlled via ATP-sensitive potassium channels and L-type calcium channels on the β-cell surface. Increase in plasma glucose closes the potassium channels and increases insulin secretion. Changes in serum potassium may prevent closure of these channels, and this may be the mechanism behind the decrease in insulin secretion noted in some studies. Hypertension is often associated with insulin resistance. In the presence of insulin resistance, pancreatic β-cells increase insulin production, maintaining euglycemia. A decrease in β-cell insulin release because of changes in potassium may lead to hyperglycemia in individuals with insulin resistance. Thiazides may also have effects on glucose homeostasis independent of those mediated via potassium. In animal models, thiazides can reduce glucose-mediated calcium entry into the β-cells decreasing insulin secretion, and in high doses, such as hydrochlorothiazide 10 mg/kg per day, can increase insulin resistance. Thiazides also cause magnesium depletion. Magnesium depletion has been associated with diabetes mellitus in several cohort studies and magnesium supplementation in diabetics is associated with a decrease in fasting glucose levels. Whether magnesium depletion also mediates thiazide-associated diabetes is unknown.

The strength of our study includes its nondiabetic population at baseline, large sample size and long duration of follow-up, as well as the large number of events providing adequate statistical power to detect differences between the 2 groups. The comparison of chlorthalidone with placebo is also advantageous, because medications such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may reduce the risk of diabetes, as well as increase serum potassium. Finally, although false-positive results because of multiple testing are always a possibility in any analysis, our study was based on an a priori hypothesis, biological plausibility, and evidence from previous association studies. Limitation of our study includes the potential for uncontrolled confounding, because diet, physical activity, and magnesium were not measured. As discussed above, there may also be residual confounding, because serum potassium may underestimate total body potassium depletion. There was also limited information available regarding potassium supplementation and changes in serum potassium after supplementation. Finally, there is the possibility, albeit unlikely, that some variable that is highly correlated with serum potassium levels is the mediating variable rather than serum potassium.

Our study has important implications for the clinical practitioner and for future research. For the practitioner, our study provides reassurance that diabetes occurring after >1 year of thiazide therapy is unlikely to be thiazide induced. In addition, nondiabetic patients currently on thiazide therapy for >1 year are unlikely to develop thiazide-induced diabetes. For future research, our study suggests that trials of potassium supplementation to prevent diabetes may not need to last for >1 year to observe a difference in outcomes.
Perspectives
Thiazide-induced changes in hypertensive individuals occurs early after initiating therapy and appears to be mediated by thiazide-induced changes in potassium. Individuals with fasting glucose $\geq 100$ mg/dL, treatment with chlorthalidone doses $>12.5$ mg/d, and a decrease in potassium from baseline $\geq 0.5$ mEq/L are at the highest risk of developing diabetes. Routine supplementation with potassium is a plausible treatment to prevent thiazide-induced diabetes. This hypothesis can and should be tested in randomized, controlled trials.

Acknowledgments
The SHEP is conducted and supported by the National Heart, Lung, and Blood Institute in collaboration with the SHEP Investigators. This article was prepared using a limited access data set obtained by the National Heart, Lung, and Blood Institute and does not necessarily reflect the opinions or views of the SHEP or the National Heart, Lung, and Blood Institute.

Sources of Funding
T.S. was supported by a Renal Disease Training Grant (5T32DK007732-12) from the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases.

Disclosures
None.

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Changes in Serum Potassium Mediate Thiazide-Induced Diabetes
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Hypertension. published online November 3, 2008;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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