Effects of potassium supplements on glucose metabolism in African Americans with prediabetes: a pilot trial

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ABSTRACT

Background: Low potassium has been identified both as a risk factor for type 2 diabetes and as a mediator of the racial disparity in diabetes risk. Low potassium could be a potentially modifiable risk factor, particularly for African Americans.

Objective: We sought to determine the effects of potassium chloride (KCl) supplements, at a commonly prescribed dose, on measures of potassium and glucose metabolism.

Design: Among African-American adults with prediabetes, we conducted a double-blinded pilot randomized controlled trial that compared the effects of 40 mEq K/d as KCl supplements with a matching placebo, taken for 3 mo, on measures of potassium and glucose metabolism, with measures collected from frequently sampled oral-glucose-tolerance tests (OGTTs).

Results: Twenty-seven of 29 recruited participants completed the trial. Participants had high adherence to the study medication (92% by pill count). Participants in both groups gained weight, with an overall mean $\pm$ SD weight gain of 1.24 ± 2.03 kg. In comparison with participants who received placebo, urine potassium but not serum potassium increased significantly among participants randomly assigned to receive KCl ($P = 0.005$ and 0.258 , respectively). At the end of the study, participants taking KCl had stable or improved fasting glucose, with a mean $\pm$ SD change in fasting glucose of -1.1 ± 8.4 mg/dL compared with an increase of 6.1 ± 7.6 mg/dL in those who received placebo ($P = 0.03$ for comparison between arms). There were no significant differences in glucose or insulin measures during the OGTT between the 2 groups, but there was a trend for improved insulin sensitivity in potassium-treated participants.

Conclusions: In this pilot trial, KCl at a dose of 40 mEq/d did not increase serum potassium significantly. However, despite weight gain, KCl prevented worsening of fasting glucose. Further studies in larger sample sizes, as well as with interventions to increase serum potassium more than was achieved with our intervention, are indicated to definitively test this potentially safe and inexpensive approach to reducing diabetes risk. This trial was registered at clinicaltrials.gov as NCT02236598. *Am J Clin Nutr* 2017;106:1431–8.

Keywords: potassium chloride, potassium, risk factor, glucose metabolism, prediabetes, African Americans

INTRODUCTION

Low potassium has been identified both as a risk factor for type 2 diabetes and as a mediator of the racial disparity in diabetes

risk, and it could potentially be a modifiable risk factor for diabetes. Several lines of evidence point to low potassium as a risk factor for type 2 diabetes, including pharmacologic studies (1), studies of human physiology (2–4), and epidemiologic studies (5–9). African Americans have a higher prevalence of both diabetes and prediabetes (10, 11), and potassium homeostasis may contribute to these disparities. Potassium homeostasis differs by race (12–16), and the association between low-normal serum potassium and increased diabetes risk has been found to be stronger in African Americans than in whites (6, 17). If relative hypokalemia is a potential risk factor for diabetes and a contributor to the racial disparity in diabetes risk, then potassium supplementation, dietary or pharmacologic, which is a potentially inexpensive, well-tolerated, and simple intervention, could improve glucose metabolism and potentially reduce diabetes risk, especially in this high-risk population.

A typical Western diet, which is low in dietary potassium, results in potassium deficiency, as reflected by serum potassium concentrations at the lower end of the normal range (14). The most accurate method of measuring total body potassium stores uses expensive whole-body counters. These expensive tests are not feasible to perform in clinical practice; however, on the basis of previous studies, serum potassium in the low end of the normal range (3.5–3.9 mEq/L; normal range typically being 3.5–5.5 mEq/L) can serve as a proxy measure of relative potassium

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Supplemental Tables 1 and 2 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at <http://ajcn.nutrition.org>.

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Abbreviations used: HbA1c, glycated hemoglobin; KCl, potassium chloride; OGTT, oral-glucose-tolerance test.

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deficiency. This concentration of serum potassium, 3.4–3.9 mEq/L, is the range of potassium that was most clearly associated with an increased diabetes risk in the cohort studies described above (5–9). A concentration <4.1 mEq/L was found to be associated with a higher risk of diabetes in an African-American cohort on the basis of our analyses of the Jackson Heart Study data (9).

On the basis of the background above, we hypothesized that increasing serum potassium concentrations in African Americans may help improve glucose metabolism and may play a role in the prevention of diabetes. In this pilot clinical trial in African Americans with low-normal serum potassium and prediabetes, we began to test this hypothesis by 1) determining the feasibility and acceptability of daily potassium supplementation, 2) determining the effects of potassium supplementation on increasing serum potassium concentrations, and 3) beginning to determine the effects of potassium supplementation at a dose commonly used in clinical practice, compared with placebo, on measures of glucose metabolism.

METHODS

Study design

The Effects of Potassium on Glucose Metabolism in African Americans study was a randomized, controlled, double-blinded pilot clinical trial to determine the impact of potassium chloride (KCl) supplementation at a dose of 40 mEq K/d compared with a matching placebo on serum and urinary potassium and on measures of glucose metabolism. The trial was approved by Duke University's Institutional Review Board and was conducted at Duke University's Stedman's Center (Durham, North Carolina; clinicaltrials.gov; identifier: NCT02236598).

Participants and eligibility criteria

To identify potentially eligible participants, the principal investigator performed chart reviews of the electronic medical records of patients from participating Duke primary care clinics who had been seen in clinic in the previous 12 mo. To be eligible for this study, participants had to be African American by self-reported race, aged ≥ 30 y, and have glycated hemoglobin (HbA1c) of 5.7–6.5% and serum potassium 3.3–4.0 mEq/L at the screening visit. Participants were deemed to be ineligible for this trial if they were taking medications that alter glycemic metabolism (e.g., metformin), had screening laboratory values with HbA1c or glucose concentrations in the diabetes range (HbA1c $> 6.5\%$ or random sugar ≥ 200 mg/dL), or evidence of chronic kidney disease with an estimated glomerular filtration rate < 60 mL/min. Participants were also ineligible if they had a history of peptic ulcer disease with past a history of either gastric or duodenal ulcer, verified with upper endoscopy; evidence of cardiac arrhythmias, unstable angina, or a cardiac event within 6 mo; congestive heart failure; or other conditions that might affect follow-up based on the discretion of the principal investigator. We excluded participants who were pregnant or who had an intention of becoming pregnant due to the effects of pregnancy on glucose homeostasis.

Interested patients who were eligible at chart review were invited to a screening visit. At the screening visit, the study purpose and procedures were reviewed, informed consent forms

were signed, and screening laboratories were drawn. If, on the basis of screening laboratory results, participants were eligible to continue in the study, they were contacted to schedule a baseline visit. They were instructed to fast for 12 h and to complete a 24-h urine collection for the baseline visit. Study participants were provided with written instructions and materials to collect the 24-h urine specimen. The instructions were to collect all urine voided within a 24-h period and store the sample in a refrigerator or cool location. On the day the sample collection was to begin, participants were instructed to empty their bladder completely during their first void of the day. This urine was not to be collected, but the time was to be noted as the “start time.” All urine for the next 24 h, until the same time the next morning, was to be captured and stored in the large collection container provided by the study team. The “end time” was recorded as the last time of urine collection for the 24-h period. The entire 24-h specimen was delivered to the study team. The total urine volume was recorded by the study team, and this value was provided to the laboratory. The specimen container was mixed thoroughly and a sample was then pulled for submission to the laboratory for analysis. The start and end date and time recorded by the participant confirmed that a full 24-h period was collected. Our recruitment target for this pilot and feasibility trial was 30 participants, which was based on available funding.

Baseline measures

Serum potassium, HbA1c, and 24-h urinary potassium, sodium, and creatinine were assessed at baseline. Participants then underwent a 3-h 75-g oral-glucose-tolerance test (OGTT). Intravenous catheters were placed in each participant's arm for convenience of sample collection. Glucose, insulin, and C-peptide measures were collected from 3-h OGTTs at minutes 0, 10, 20, 30, 60, 90, 120, and 180.

During the baseline OGTT, participants were provided with a laptop to complete an online 24-h dietary recall instrument, the Automated Self-administered 24-h Recall (ASA24; <https://epi.grants.cancer.gov/asa24/>). The ASA24 system is a Web-based tool that enables multiple automated self-administered 24-h recalls. Participants completed this instrument once during the baseline 3-h OGTT; they were asked to complete a second recall from home during the following week.

Randomization

After completion of the OGTT, participants were stratified by sex and randomly assigned 1:1 in blocks of 4 to receive either KCl or placebo. The randomization scheme was created by the Investigational Drug Services Unit of Duke University Hospital and was concealed from the study team.

Intervention

Potassium supplement

KCl (Klor-Con M10; Cardinal Health) is an immediately dispersing, extended-release oral dosage form of KCl containing 750 mg microencapsulated KCl, a US Pharmacopeia equivalent of 10 mEq K/tablet. Participants were instructed to take two 10-mEq tablets 2 times/d in a blinded encapsulated form.

FIGURE 1 Consolidated Standards of Reporting Trials 2010 flow diagram for enrollment. OGTT, oral-glucose-tolerance test.

Placebo

An inert powder of maltodextrin was used as the placebo substance and was identically encapsulated as the KCl intervention tablets to maintain blinding. Each placebo capsule contained, on average, 0.34 g maltodextrin, which is equivalent to 0.32 g carbohydrates or 1.3 kcal. Participants were asked to take 2 capsules 2 times/d. Participants were instructed to take the study medication 2 times/d with a meal and with a full 8-ounce (237 mL) glass of water. They were also instructed not to change their diet or physical activity pattern during the study period and to try to maintain their weight during this 12-wk period.

Participants were asked to return after 2 wk to assess tolerance and adherence to the study medication and to get additional medication. Adherence was measured by pill count. At the 2-wk visit, laboratory samples were drawn to reassess serum potassium and renal function to ensure the safety of the intervention. Participants were also asked to return 6 wk after the baseline visit to assess adherence by pill count and to get additional medication.

Final measures

At week 12, participants were asked to arrive after an overnight fast, and they underwent a final 3-h OGTT in the same manner as performed at the baseline OGTT. Blood samples were obtained for final measurements of serum potassium and HbA1c. Participants were also asked to complete a 24-h urine collection just

before this final OGTT. A pill count was performed to assess adherence to study medication.

Measures of covariates

Repeated blood pressure readings were taken during the baseline and final OGTTs. An automatic oscillometric blood pressure machine was used with an appropriately sized cuff. Blood pressure was measured twice, 5 min apart while the participant was seated comfortably during the OGTT procedure, between the 60- and 90-min time points. The average of the 2 measures was used for analyses. A stadiometer was used to measure height at the baseline examination. The same calibrated electronic digital scale was used to measure participants' weight at the baseline and final visits. Participants were asked to bring in their medication bottles at the screening visit. Medications and medical history were reviewed by the study coordinator at the screening visit.

Laboratory analyses

HbA1c measures were measured at LabCorp by using Roche Tina-quant methodology. Serum potassium was measured at LabCorp with the use of enzymatic, kinetic Jaffe, ion-selective electrode, colorimetric methodology. Twenty-four-hour urinary sodium and potassium measures were assessed by using ion-selective electrode and flame photometer methodology, and 24-h urinary creatinine was assessed by using kinetic methodology. Urinary measures were also performed by LabCorp.

TABLE 1
Baseline characteristics of participants¹

	Potassium supplement	Placebo	P ²
<i>n</i>	15	12	
Age, y	56.9 ± 11.0	52.7 ± 8.9	0.304
Female, <i>n</i> (%)	10 (66.7)	8 (66.7)	1.000
BMI, kg/m ²	34.3 ± 5.4	35.1 ± 5.2	0.717
Baseline systolic blood pressure, mm Hg	128.3 ± 15.0	127.7 ± 10.1	0.902
Screen serum potassium, mEq/L	3.8 ± 0.2	3.7 ± 0.2	0.274 ³
Screen serum sodium, mEq/L	141.5 ± 2.4	141.2 ± 1.5	0.469 ³
Screen eGFR, mL · min ⁻¹ · 1.73 m ⁻²	98.5 ± 19.9	94.4 ± 18.0	0.582
Diuretic use, <i>n</i> (%)	4 (27)	7 (58)	0.096
Potassium supplement use, <i>n</i> (%)	3 (20)	2 (17)	0.825
ACE-I/ARB use, <i>n</i> (%)	5 (33)	4 (33)	1.000
Dietary potassium intake ⁴			
mg/d	2456.0 ± 1013.3	2357.5 ± 669.3	0.791
mg/2000 kcal	2473.0 ± 678.8	2320.3 ± 719.8	0.602
Screen HbA1c, %	6.1 ± 0.15	6.0 ± 0.25	0.159
Fasting glucose, mg/dL	100.4 ± 10.1	94.9 ± 7.2	0.127
Glucose			
2-h AUC	16,601 ± 3072.3	15,504.6 ± 1981.1	0.295
1-h, mg/dL	154.1 ± 33.7	138.6 ± 26.9	0.207
2-h, mg/dL	125.9 ± 34.1	127.2 ± 27.5	0.920
2-h Insulin AUC	430,267 ± 175,280.6	403,431.7 ± 239,040.8	0.739
2-h C-peptide AUC	615.8 ± 180.4	584.3 ± 188.2	0.663
Insulinogenic index	1.8 ± 1.5	0.5 ± 4.7	0.290
Matsuda insulin sensitivity index	3.5 ± 1.7	4.1 ± 2.2	0.442
Disposition index	6.3 ± 6.3	0.3 ± 19.9	0.284
Utz disposition index	0.2 ± 0.1	0.01 ± 0.5	0.263

¹ Values are means ± SDs unless otherwise indicated. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin.

² Derived by using 2-sample *t* tests (pooled) or chi-square testing, except where otherwise indicated.

³ Derived by using Mann-Whitney test.

⁴ Excluding those with caloric intakes <400 and >4000 kcal (*n* = 24: 14 in the potassium-supplement arm and 10 in placebo arm).

For plasma collected from the OGTT, glucose was measured on a Beckman DxC600 analyzer with the use of standard enzymatic reagents from Beckman. Human insulin was measured by electrochemiluminescent immunoassay on an SI-2400 imager from Meso Scale Discovery. Human C-peptide was measured by using an ELISA from Millipore on a Molecular Devices M2e plate reader. These OGTT measures were performed by the immunoassay laboratory at the Duke Molecular Physiology Institute.

Outcomes

Changes in potassium measures, including changes in serum potassium and in 24-h urinary potassium, change in weight, and adherence to the intervention on the basis of pill counts, were determined at the end of the 12-wk study period. The primary endpoint for this trial was change in glucose tolerance, as measured by 2-h change in glucose AUC (measured via the trapezoidal method) from the 3-h OGTT. Secondary endpoints included changes in fasting, 1- and 2-h postchallenge glucose concentrations, measurements of insulin secretion and insulin sensitivity, as well as change in blood pressure (18–20).

Statistical analyses

Baseline characteristics by treatment group were compared by using Mann-Whitney tests or 2-sample *t* tests, as appropriate, for

continuous measures and chi-square tests for categorical variables. Primary and secondary outcomes by treatment group were compared by using 2-sample *t* tests. In sensitivity analyses, the intervention effect on the outcome of interest was assessed by using ANCOVA, adjusted for baseline measures of the outcome of interest (**Supplemental Tables 1 and 2**).

Because of the small sample size and the recognition that data from 1 or 2 participants could skew the data, we decided a priori to conduct sensitivity analyses by excluding participants with outlying data, particularly with regard to potassium measures, weight change, or pill adherence. Data analyses were performed by using STATVIEW 2 (SAS Institute) and R 3.3.0 (R Core Team).

RESULTS

Figure 1 depicts the CONSORT (Consolidated Standards of Reporting Trials) diagram for recruitment for this trial. Participants were recruited starting in January 2015 through November 2015, with the last study visit being completed at the end of February 2016. Of the 360 participants who were contacted to participate in the study, 60 (17%) expressed interest in the study and signed an informed consent. Of these, 29 participants were deemed eligible on the basis of the results of the screening laboratories. Twenty-seven participants were randomly assigned, completed the study, and had baseline and end-of-study

TABLE 2Potassium measures, pill adherence, and weight change in participants at 12 wk¹

	Potassium supplement	Placebo	P ²
<i>n</i>	15	12	
Adherence, % of pills prescribed	91.4 ± 8.7	93.6 ± 9.3	0.538
Weight change, kg	1.47 ± 1.9	0.97 ± 2.2	0.535
Final serum potassium, mEq/L	4.00 ± 0.2*	3.81 ± 0.2*	0.041*
Change in serum potassium, mEq/L	0.18 ± 0.3	0.07 ± 0.2	0.258
Change in urine potassium, mmol/24 h	32.12 ± 33.3*	−8.69 ± 23.1*	0.005*

¹ Values are means ± SDs unless otherwise indicated. *Statistically significant, $\alpha = 0.05$.² Derived by using 2-sample *t* tests.

measurements. Baseline characteristics of these 27 participants are presented by treatment group in **Table 1**. Sixty-seven percent of the randomly assigned participants were female. Among these participants, mean ± SD values were as follows—age: 55 ± 10.1 y; BMI (kg/m²): 34.6 ± 5.1; serum potassium: 3.8 ± 0.2 mEq/L; and HbA1c: 6.1% ± 0.2%.

Potassium measures, change in weight, and pill adherence

Table 2 shows changes in potassium measures, changes in weight, and adherence to study medication based on pill count over the 12-wk study period. Adherence, based on pill count, was high among both groups, with an overall mean compliance of 92%. Compared with those taking placebo, the final serum potassium concentration was significantly higher for those in the potassium-supplement arm. However, the mean ± SD final potassium concentration for those taking the potassium supplements was lower than expected at 4.0 ± 0.24 mEq/L. In addition, the change in serum potassium over the 12-wk study period (final − baseline) was not significantly different between the 2 study arms (**Table 2**). Compared with those taking placebo, the change in 24-h urinary potassium (final − baseline) increased significantly among those taking potassium supplements (**Table 2**). Finally, despite encouraging maintenance of lifestyle, participants in both groups gained weight during the course of the study (**Table 2**).

Final outcomes

The primary outcome for the trial was change in overall glucose tolerance as measured by glucose AUC over the 2 h after ingestion of the 75-g glucose drink. Over the 12-wk study period, participants in both groups showed a worsening of glucose tolerance reflected by an increase in glucose AUC (potassium supplements compared with placebo: 328 ± 1780 compared with 1000 ± 2379; $P = 0.41$) (**Table 3**).

At the end of the study, participants taking potassium supplements had significantly better fasting glucose, with a mean ± SD change in fasting glucose of −1.1 ± 8.4 mg/dL for those taking KCl compared with 6.1 ± 7.6 mg/dL for those taking placebo ($P = 0.03$) (**Table 3**). Among participants taking KCl, 8 of the 15 participants experienced improvements in fasting glucose ranging from −1 to −19 mg/dL. Among participants taking placebo, only 2 of 12 participants experienced improvements in fasting glucose of −1 and −3 mg/dL. Compared with placebo, participants taking potassium supplements showed no significant differences in other secondary outcomes (**Table 3**).

Sensitivity analyses

We identified 2 participants with outlying data, both of whom were in the potassium-supplement arm, whom we excluded in our sensitivity analyses. One participant gained 14.7 pounds (6.7 kg) during the study period, which differed from the other

TABLE 3Final outcomes in participants at 12 wk¹

	Potassium supplement	Placebo	P ²
<i>n</i>	15	12	
Change			
Fasting glucose, mg/dL	−1.07 ± 8.40*	6.08 ± 7.61*	0.031*
2-h Glucose AUC	328.00 ± 1779.67	1000.00 ± 2378.46	0.409
1-h Glucose, mg/dL	0.80 ± 31.36	14.17 ± 37.07	0.320
2-h Glucose, mg/dL	3.60 ± 25.82	0.75 ± 24.53	0.773
2-h Insulin AUC	71,444 ± 213,221	149,327 ± 378,900	0.506
2-h C-peptide AUC	62.07 ± 201.56	85.74 ± 132.77	0.729
Insulinogenic index	0.07 ± 1.57	1.12 ± 4.30	0.389
Matsuda insulin sensitivity index	−0.03 ± 1.49	−0.87 ± 1.13	0.122
Disposition index	−0.64 ± 5.36	−1.26 ± 4.87	0.759
Utz disposition index	−0.01 ± 0.11	−0.05 ± 0.10	0.363
HbA1c, ³ %	−0.02 ± 0.32	−0.01 ± 0.23	0.916
Mean systolic blood pressure, mm Hg	−0.17 ± 12.68	−3.58 ± 10.31	0.458

¹ Values are means ± SDs unless otherwise indicated. *Statistically significant, $\alpha = 0.05$.² Derived by using 2-sample *t* tests.³ HbA1c, glycated hemoglobin.

participants by >3 SDs of mean weight change (Table 2). The other participant was excluded because he was the only participant in the potassium-supplement arm whose final serum and urinary potassium measures decreased compared with his own baseline measures. This indicated that he was either given the incorrect study medication or was not actually taking the study medication as reported. After the exclusion of these 2 participants with outlying data, we found a strengthening of the main results (Table 4). Compared with placebo, those participants taking potassium supplements continued to show significantly lower fasting glucose (mean $\pm$ SD change in fasting glucose of potassium supplements compared with placebo: -2.2 ± 8.4 compared with 6.1 ± 7.6 mg/dL; $P = 0.02$) as well as trends in improvement in insulin sensitivity and disposition indexes (Table 4).

DISCUSSION

In this pilot clinical trial in African-American participants with low-normal serum potassium and prediabetes, as measured by HbA1c, we tested the effects of potassium supplements, in the form of 40 mEq KCl/d, compared with placebo on measures of glucose metabolism. We found that participants tolerated the study medication well and had high adherence on the basis of pill count as well as 24-h urinary potassium measures, which strongly correlate with potassium intake (14). However, we also found that, compared with placebo, the intervention did not increase serum potassium significantly and did not achieve a theoretical target of ≥ 4.1 mEq/L, which, in a cohort study in African Americans, has been associated with a lower risk of diabetes (9). Despite the minimal effect on serum potassium, we did find trends to suggest that potassium supplementation may have favorable effects on glucose metabolism. Over a 12-wk study period, compared with placebo, those participants taking potassium supplements had more favorable measures of fasting glucose and showed trends in improvements in insulin sensitivity and disposition indexes (Tables 3 and 4). On average, participants in both arms gained weight during the study period;

however, despite the weight gain, compared with placebo, potassium supplementation seemed to prevent deterioration in both fasting glucose and insulin sensitivity. This suggests that potassium supplementation, which is a well-tolerated and inexpensive intervention, should be studied further in an adequately powered clinical trial, and likely should be studied at higher doses to determine more definitively its effects on glucose metabolism and its longer-term effects on diabetes risk.

The association between serum potassium and abnormal glucose metabolism has been noted for many decades, with the finding that abnormal glucose tolerance is associated with conditions that lead to low potassium or hypokalemia, such as primary hyperaldosteronism (21), Barter syndrome (22), and more commonly, the use of thiazide diuretics (23–26). The physiologic mechanism that accounts for these associations has been studied in small experimental studies. On the basis of the experimental studies, some of which used techniques to include whole-body potassium counters and hyperglycemic clamps in participants with normal glucose tolerance, the induction of hypokalemia led to impairments in insulin secretion and the development of impaired glucose tolerance (2–4). In one of these studies, potassium supplementation to maintain serum potassium concentrations in the normal range prevented the development of impairments in glucose tolerance (3).

Although the physiologic experiments described above, which were conducted in participants with normal glucose tolerance, suggest that hypokalemia can lead to abnormal glucose tolerance due to decreased insulin secretion that can be corrected with potassium supplementation, our pilot trial, which was conducted in participants with prediabetes, did not show an increase in insulin secretion (based on insulin AUC or insulinogenic index) with potassium supplementation. Rather, we found that potassium supplementation seemed to have favorable impacts on insulin sensitivity (based on the Matsuda sensitivity index), rather than insulin secretion, with overall favorable impacts on fasting glucose and disposition indexes.

TABLE 4

Final outcomes from sensitivity analyses of participants at 12 wk, excluding outliers¹

	Potassium supplement	Placebo	P^2
<i>n</i>	13	12	
Change			
Fasting glucose, mg/dL	$-2.15 \pm 8.37^*$	$6.08 \pm 7.61^*$	0.017*
2-h Glucose AUC	18.85 ± 1675.05	1000 ± 2378.46	0.242
1-h Glucose, mg/dL	-2.77 ± 31.37	14.17 ± 37.07	0.229
2-h Glucose, mg/dL	1.31 ± 26.83	0.75 ± 24.53	0.957
2-h Insulin AUC	$45,982.69 \pm 209,709.24$	$149,326.67 \pm 378,899.79$	0.403
2-h C-peptide AUC	35.00 ± 198.62	85.74 ± 132.77	0.464
Insulinogenic index	0.27 ± 1.37	1.12 ± 4.30	0.506
Matsuda insulin sensitivity	0.11 ± 1.54	-0.87 ± 1.13	0.086
Disposition index	0.71 ± 2.39	-1.26 ± 4.87	0.206
Utz disposition index	0.02 ± 0.07	-0.05 ± 0.10	0.068
HbA1c, ³ %	0.02 ± 0.33	-0.01 ± 0.23	0.837
Mean systolic blood pressure, mm Hg	-1.31 ± 11.16	-3.58 ± 10.31	0.602

¹ Values are means $\pm$ SDs unless otherwise indicated. Outliers included one participant who gained 14.7 pounds (6.7 kg) during the study period, and another participant in the potassium-supplement arm whose final serum and urinary potassium measures decreased compared with his own baseline measures during the study period. *Statistically significant, $\alpha = 0.05$.

² Derived by using 2-sample *t* tests.

³ HbA1c, glycated hemoglobin.

Although this pilot trial indicates favorable effects of potassium supplementation on measures of fasting glucose, we recognize limitations in our trial design. First, although the trial participants were randomly assigned, there were more participants taking diuretics in the placebo arm than in the supplement arm. Although the number was not significant ($P = 0.09$), because of the small sample size this difference still could have affected the results. Second, our choice of maltodextrin as a placebo contained a small amount of free glucose; however, this amount was fairly minimal. Third, our dose of 40 mEq KCl/d is equivalent to ~ 1560 mg dietary K. With this dose, we had hoped to have participants achieve the Adequate Intake of dietary potassium of 4700 mg/d. On the basis of mean dietary potassium intake from the participants' baseline 24-h recall, even with the potassium supplements, most participants would not have achieved this Adequate Intake level. In addition, with our dose of KCl, the participants in the active arm did not achieve a significant increase in serum potassium and their mean serum potassium at the end of the trial was only 4.0 mEq/L. In another randomized controlled trial in 101 participants randomly assigned to receive KCl or placebo that evaluated the effects of KCl on blood pressure, KCl doses of 120 mEq/d were well tolerated and did not lead to hyperkalemia but did lead to a mean serum potassium concentration higher than achieved in our pilot trial (27). This higher dose of KCl was found to have blood pressure-lowering effects; however, the effects of this dose of KCl on glucose metabolism were not evaluated. In another small trial in 11 participants with combined impaired fasting glucose and impaired glucose tolerance, doses of KCl or potassium citrate of 90 mEq/d were well tolerated, with minimal effects on plasma potassium but with favorable effects on β cell function and, for potassium citrate, on insulin sensitivity as well (28). In clinical practice, providers generally do not prescribe doses >40 mEq/d (29). This pilot trial and these other trials suggest that doses >40 mEq/d would be safe in patients who are similar to the study participants and may have more health benefits than the lower doses that are generally currently prescribed.

Finally, in this pilot and feasibility study, we must address the important limitation of the small sample size. The sample size was chosen on the basis of the finances available to fund this trial. Although we observed a significant change in fasting glucose, this study was not designed to be an adequately powered trial to detect significant differences in our primary outcome of change in 2-h glucose AUC. As expected, we did not find significant changes in most of our measures of glucose metabolism. However, we feel, as do other biostatisticians, that even non-significant findings can indicate trends in effect and can indicate whether or not further study should be conducted in this area (30). In this pilot trial, we feel that the findings taken as a whole, and especially the findings related to fasting glucose and insulin sensitivity, suggest that further study, in larger sample sizes, seems warranted.

On the basis of our and others' epidemiologic studies, mean serum potassium concentrations >4.0 mEq/L seem to be associated with a lower risk of diabetes. Therefore, to determine whether increasing potassium concentrations has a favorable impact on glucose metabolism, interventions to increase serum potassium >4.0 mEq/L, either through higher doses of KCl or other interventions, pharmacologic or dietary, should be tested. Because potassium is important for other health conditions,

particularly blood pressure, and because interventions to increase potassium are simple and inexpensive, it will be important to definitively determine whether increasing serum potassium can help fight the diabetes epidemic.

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