Effect on Blood Pressure of Potassium, Calcium, and Magnesium in Women With Low Habitual Intake

Effect on Blood Pressure of Potassium, Calcium, and Magnesium in Women With Low Habitual Intake

Frank M. Sacks, Walter C. Willett, Angela Smith, Lisa E. Brown, Bernard Rosner, Thomas J. Moore

Abstract—In populations, dietary intakes of potassium, calcium, and magnesium each have been inversely associated with blood pressure. However, most clinical trials in normotensive populations have not found that dietary supplements of these minerals lowered blood pressure. We tested the hypothesis that normotensive persons who have low habitual intake of these minerals would be particularly responsive to supplementation. Three hundred normotensive women in the Nurses Health Study II (mean age, 39 years), whose reported intakes of potassium, calcium, and magnesium were between the 10th and 15th percentiles, received for 16 weeks' duration daily supplements of either potassium 40 mmol, calcium 30 mmol (1200 mg), magnesium 14 mmol (336 mg), all three minerals together or placebos. At baseline, mean (±SD) 24-hour ambulatory blood pressures were 116±8 and 73±6 mm Hg systolic and diastolic, respectively, and mean dietary intakes of potassium, calcium, and magnesium were 62±20 mmol/d, 638±265 mg/d, and 239±79 mg/d, respectively. The mean differences (with 95% confidence intervals) of the changes in systolic and diastolic blood pressures between the treatment and placebo groups were significant for potassium, −2.0 (−3.7 to −0.3) and −1.7 (−3.0 to −0.4), but not for calcium, −0.6 (−2.2 to 1.0) and −0.7 (−2.0 to 0.6), or for magnesium, −0.9 (−2.6 to 0.8) and −0.7 (−2.2 to 0.8). The administration of calcium and magnesium with potassium did not enhance the effect of potassium alone; and the changes in blood pressure were not significant −1.3 (−3.0 to 0.4) and −0.9 (−2.2 to 0.4). In conclusion, potassium, but not calcium or magnesium supplements, has a modest blood pressure–lowering effect in normotensive persons with low dietary intake. This study strengthens evidence for the importance of potassium for blood pressure regulation in the general population. **(*Hypertension*. 1998;31[part 1]:131-138.)**

Key Words: blood pressure ■ potassium ■ calcium ■ magnesium ■ diet ■ blood pressure monitoring, ambulatory

Dietary potassium, calcium, and magnesium have each been inversely associated with blood pressure in populations.[1–15] Since these cations exist together in commonly eaten foods such as fruits, nuts, vegetables, cereals, and dairy products, their intakes are highly correlated. This collinearity makes it difficult in epidemiological studies to distinguish which among these dietary cations has a causal role in blood pressure regulation.[1] Meta-analysis of clinical trials found a significant blood pressure–lowering effect (−5.9/−3.4 mm Hg) for potassium supplementation in hypertensive but not in normotensive persons.[10,16] Meta-analysis suggested that calcium supplementation has a small effect (−1.7 mm) on systolic blood pressure in hypertensive but not normotensive patients.[17,18] Magnesium produced inconsistent results in trials of hypertensives,[19–28] and no effect in normotensives.[29,30] The lack of effect of mineral supplements in clinical trials of normotensives is inconsistent with the significant associations in epidemiological studies, since normotensive persons comprise the vast majority of the population samples.

One possible explanation for the divergence in findings between the observational epidemiologic studies and the clinical trials in normotensive persons is that a subset of the population that is relatively deficient from low intake of minerals may be particularly responsive to supplementation. Epidemiological studies tend to compare those in the lowest category of intake, which serves as a point of reference, with persons having average or high intake. In contrast, most trials have tested the effect of raising an average intake to a high intake. An alternative explanation is that these minerals work in concert to reduce blood pressure and that they would be more effective when given together. To explore both possibilities, we conducted a clinical trial of potassium, magnesium, and calcium supplements, given singly and together, to participants in the Nurses Health Study II who reported habitually low intakes of these minerals.

Methods

Subjects

The subjects were US nurses participating in the Nurses Health Study II, an epidemiological cohort study. Prospective participants for this trial were identified as having potassium, magnesium, and calcium intakes all below the 30th percentile on a validated food frequency questionnaire[31] administered 1 to 2 years before the study, and confirmed to be <50th percentile on repeat administration during

Received April 30, 1997; first decision May 19, 1997; revision accepted August 17, 1997.

From the Department of Nutrition, Harvard School of Public Health (F.M.S., W.C.W., L.E.B.), and the Channing Laboratory (F.M.S., W.C.W., A.S., L.E.B., B.R.), and Endocrine Hypertension Division (T.J.M.), Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, Mass.

Reprint requests to Dr Sacks, Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave, Boston, MA 02115.

E-mail fsacks@hsph.harvard.edu

screening. The food frequency questionnaire measured typical intake over a 1-year period. Initially, nurses whose intakes were in the 10th percentile were invited to participate, and after the number of enrollees from this group was determined, those below the 20% percentile and finally those below the 30% percentile were screened. This strategy enriched the study population with those in the lower part of the eligibility range for intake. Exclusion criteria included reported diastolic blood pressure <65 mm Hg; hypertension; body mass index >32 kg/m^2; insulin-dependent diabetes; cardiovascular disease; renal failure; medications that affect blood pressure, weight-loss diets, use of nutritional supplements of calcium, magnesium, or potassium (including antacid preparations); and alcohol intake >50 g/d.

From a total of 3442 persons who were invited to be screened for eligibility, 1004 (29%) expressed interest. Of these, 250 (25%) were excluded from further participation for the following reasons: hypertension, other major illness, use of medication that affects blood pressure (53 [5%]), planning to become pregnant (56 [6%]), obesity (49 [5%]), unable to contact again (38 [4%]), and declined to participate (47 [5%]). The remaining 754 nurses were invited for further screening, and 583 expressed interest again. Of these, 393 were screened to meet the enrollment goal of 320, and 321 (82%) were randomized. Twenty-one participants withdrew before the midpoint and were not available for follow-up measurements. Therefore, the final study population was 300 women who completed baseline and midpoint measurements. Of these, 290 completed the end-of-study measurements. This study was approved by the institutional review board at Brigham and Women's Hospital, and the subjects gave informed consent.

Study Design

The design was a randomized, parallel group trial with four groups receiving dietary supplements and a fifth receiving placebos, all under double-blind conditions for 16 weeks. Potentially eligible participants were enrolled in a 4-week run-in phase during which placebo pills (magnesium-placebo, two capsules, twice daily) were prescribed. During the run-in period, they received 24-hour ambulatory blood pressure monitoring, and collected a 24-hour urine sample. Subjects were considered eligible if they had a pill count indicating that >90% of their assigned pills were taken. Subjects who had baseline systolic blood pressure above 160 mm Hg or diastolic blood pressure >95 mm Hg were excluded and advised to see their physicians. They all agreed to leave their habitual diet including sodium intake unchanged and to not take mineral supplements.

The participants were randomized into one of five groups: potassium chloride 40 mmol daily (K-Dur 20 mmol twice daily, Key Pharmaceutical); calcium carbonate 1200 mg daily (Caltrate 600 mg twice daily, Lederle Laboratories); magnesium lactate 336 mg daily (two 84-mg sustained release tablets twice daily, Niche' Pharmaceuticals); the combination of these minerals and doses; and placebo tablets that matched the calcium tablets. The placebo group received twice the number of participants as the four treatment groups to improve statistical power.[32] Pills were distributed in calendar packs. These doses of supplements were intended to raise the intake of each mineral above the 90th percentile of the Nurses Health Study I.[7] Follow-up information was collected at the midpoint (8 weeks) and end of study (16 weeks): ambulatory 24-hour blood pressure, 24-hour urine, body weight, health and side effects questionnaire, and pill counts. At the end of the trial, the dietary questionnaire was administered to quantify intake during the trial.

Measurements

Twenty-eight ambulatory blood pressure monitors (SpaceLabs model #90207, SpaceLabs Medical Inc) were leased for the duration of the study. A monitor was delivered to each participant by express mail and returned within 48 hours. Instructions were sent to the subjects along with the monitors, and a staff member called each participant to confirm her understanding. The 24-hour monitoring for each of the three measurement periods took place on a workday. For nurses who were not working, monitoring took place on a specific weekday. Blood pressure was measured every 30 minutes during waking hours (generally from 6 AM to 10 PM for day-shift workers, or from 5 PM to 10 AM for night-shift workers), and every 1 hour during sleep (generally from 12 AM to 7 AM for day-shift workers or from 10 AM to 5 PM for night-shift workers). The blood pressure machine automatically entered the blood pressure data on computer tape that was later converted to an ASCII file at the study office.

The nurses recorded the volume of their 24-hour urine collection and mailed a 10 mL sample. Urine samples were analyzed by atomic absorption spectrophotometry for calcium and magnesium content and by autoanalyzer for sodium, potassium, and creatinine content at the Core Laboratory of the Clinical Research Center, Brigham and Women's Hospital.

Data Analysis

Blood pressure was averaged for each hour, and then the mean for the 24 hourly pressures was computed. The primary outcome variable was the change in mean 24-hour diastolic blood pressure from baseline during treatment defined as the average of the 8- and 16-week measurements. Participants were included in the analysis who completed the 8-week but not the 16-week blood pressure measurements. For these subjects, the 8-week measurements were used for the outcome variable. The General Linear Models multiple regression procedure of the Statistical Analysis System was used to determine whether mean change in blood pressure from baseline in each of the four treatment groups was different from the mean change in the placebo group.[33] In secondary analyses, the blood pressure changes were adjusted for the influence of covariates, including baseline blood pressure; age; baseline urinary excretion of potassium, magnesium, and calcium; and baseline dietary intake of these cations.

Results

Three hundred of the 321 randomized participants (93%) completed baseline and midpoint measurements. Reasons for withdrawal from the study were difficulty swallowing the pills (3), pregnancy (4), illness (4), family/social problems (5), and possible adverse reactions to the supplements (5). Mean age was 39±5 (SD) years, mean body mass index was 23±3 kg/m^2, and whites comprised 96% of the group (Table 1). There were no important differences among the treatment groups in characteristics at baseline (Table 1). Ten participants withdrew between the midpoint and end and therefore did not provide final measurements. Reasons for withdrawal were pregnancy (1), possible side effects (2), development of a concomitant medical problem (2), and various personal issues (5). These subjects were included in the primary analysis of blood pressure changes. At baseline, mean daily dietary intake of potassium was 2433±792 mg (62±20 mmol), calcium 638±265 mg, and magnesium 239±79 mg; there were no appreciable differences among the groups (Table 2). These intakes corresponded to the following percentiles in the Nurses Health Study II population from which the participants in the present study were selected: potassium, 10th; magnesium, 17th; and calcium, 10th. The addition of the supplements raised the mean total daily intake of potassium to 4072 mg (102 mmol), magnesium to 585 mg, and calcium to 1835 g. These intakes correspond to the following percentiles in the Nurses Health Study II population: potassium 90th, magnesium 95th, and calcium >95th.

Baseline 24-hour urinary potassium excretion was 41±16 mmol, calcium 4.8±2.2 mmol, and magnesium 3.9±1.3 mmol and was similar across the four treatment groups (Table 3). Urinary excretion of potassium, calcium, and magnesium increased significantly in the groups that received these minerals as supplements, compared with the placebo

TABLE 1. Characteristics of the Participants

Characteristics	Supplement Group				
	Mg (n=50)	Ca (n=53)	K (n=49)	Ca/Mg/K (n=45)	Placebo (n=103)
Race					
White	50	51	47	42	97
Black	0	1	1	3	2
Hispanic	0	1	0	0	1
Asian	0	0	1	0	3
Mean age	39±4.4	39±5.0	39±4.4	38±5.0	38±4.5
Smokers					
Current	4	6	6	3	17
Former	11	9	5	10	16
Weight, kg	63.6±10.6	63.8±9.9	65.4±10.8	64.0±10.0	63.4±9.7
BMI, kg/m^2	23.5±3.5	23.5±3.0	23.8±3.7	23.3±3.7	23.2±3.1

BMI indicates body mass index. Subjects are included who completed the midpoint blood pressure measurements. Units are numbers of subjects for sex, race, and smokers; otherwise mean±SD.

group (Table 3). According to pill counts, the patients in all groups took 94% to 96% of their assigned pills. The increase in potassium excretion, 29 mmol, was 76% of the ingested dose, 38 mmol (40 mmol administered × 96% compliance by pill count). The increases in the group that received all three minerals were similar to those in the groups that received a single mineral supplement. Sodium excretion was similar across treatment groups, averaging 135 mmol/d.

Mean 24-hour blood pressure at baseline was 116±8 mm Hg systolic and 73±6 mm Hg diastolic, and was

TABLE 2. Mean Dietary Intake

Study Period	Supplement Group				
	Mg	Ca	K	Ca/Mg/K	Placebo
Baseline					
Calories	1968±608	2025±753	1985±552	2047±500	1904±654
Protein	79±22 (16.1)	80±30 (15.8)	78±21 (15.7)	81±23 (15.8)	75±29 (15.8)
Carbohydrate	258±101 (52.4)	264±115 (52.1)	254±93 (51.1)	265±68 (51.8)	245±91 (51.5)
Total fat	69±23 (31.6)	73±27 (32.4)	74±21 (33.6)	75±23 (33.0)	70±28 (33.0)
Alcohol	3±5 (1.1)	3±7 (1.0)	2±4 (0.7)†	3±3 (1.0)†	4±6 (1.5)
Fiber	16±6	17±7	16±6	17±6	16±7
Calcium	620±242	646±282	667±274	657±253	622±270
Magnesium	234±69	244±87	231±67	248±74	238±88
Potassium	2386±694	2465±982	2389±629	2507±739	2426±831
n	50	53	49	45	103
Closing					
Calories	1933±664	1919±643	1908±549	2048±621†	1823±538
Protein	84±29 (17.4)	77±28 (16.1)	82±27 (17.2)	84±27 (16.4)	75±26 (16.5)
Carbohydrate	244±103 (50.5)	245±94 (51.1)	235±87 (49.3)*	265±83 (51.8)	233±80 (51.1)
Total fat	69±25 (32.1)	70±26 (32.8)	71±21 (33.5)	73±29 (32.1)	65±23 (32.1)
Alcohol	2±3 (0.7)	3±7 (1.1)	3±7 (1.1)	3±5 (1.0)	3±6 (1.1)
Fiber	17±8	17±7	16±6	18±5†	16±6
Calcium	638±270	1823±239‡	687±330†	1846±244‡	563±203*
Magnesium	582±87‡	244±110	243±79	588±83‡	229±76
Potassium	2416±887	2426±904	3963±794‡	4181±861‡	2329±734
n	48	51	45	43	102

Values are mean±SD (% of total calories); units are as follows: calories, kcal/d; protein, carbohydrate, total fat, fiber, and alcohol; g/d; and calcium, magnesium, and potassium; mg/d.

*$P<.05$ for within group differences (closing−baseline.

†$P<.05$; ‡$P<.01$ for dietary changes (closing−baseline) for active treatment group compared with placebo group.

TABLE 3. Urinary Excretion of Electrolytes and Creatinine

Treatment	Baseline	Treatment	Change
Mg			
Calcium	5.4±2.6†	5.2±2.4†	−0.2±1.7
Magnesium	4.1±1.2	6.2±2.0**‡	2.1±1.7‡
Sodium	124±37	137±55	14±49†
Potassium	39±14	42±11	3±14
Creatinine[1]	1.2±0.2	1.2±0.6	0.0±0.6
Creatinine[2]	10.1±2.0	10.3±5.4	0.2±5.2
Ca			
Calcium	4.7±2.2	5.7±2.2**‡	1.0±1.8‡
Magnesium	3.5±1.3	3.4±1.1	−0.0±1.2
Sodium	127±51	123±43	−4±47
Potassium	40±12	41±11	1±13
Creatinine[1]	1.1±0.3	1.0±0.3	−0.0±0.3
Creatinine[2]	9.5±2.7	9.2±2.2	−0.3±2.5
K			
Calcium	4.8±2.7	4.3±2.7	−0.5±2.0
Magnesium	4.0±1.3	4.0±1.9	−0.0±1.4
Sodium	142±70	141±79	−1±54
Potassium	42±25	72±37**‡	29±22‡
Creatinine[1]	1.2±0.6	1.1±0.3	−0.1±0.4
Creatinine[2]	10.6±5.2	10.0±2.8	−0.6±3.6
Ca/Mg/K			
Calcium	4.8±2.0	5.6±2.1*‡	0.9±1.9‡
Magnesium	4.1±1.7	6.0±1.6**‡	1.9±1.9‡
Sodium	132±43	125±51	−7±51
Potassium	43±14	71±22**‡	28±20‡
Creatinine[1]	1.1±0.3	1.1±0.2	−0.0±0.3
Creatinine[2]	10.0±2.2	9.7±2.1	−0.3±2.2
Placebo			
Calcium	4.5±1.7	4.2±1.8	−0.2±1.4
Magnesium	3.9±1.2	3.8±1.4	−0.1±1.6
Sodium	137±52	130±38	−7±64
Potassium	43±14	42±15	−1±18
Creatinine[1]	1.1±0.3	1.2±0.6	0.1±0.6
Creatinine[2]	9.8±2.6	10.3±5.5	0.6±5.3

Between Group Differences: †$P<.05$, ‡$P<.01$ vs placebo.
Within Group Differences: *$P<.05$, **$P<.01$.
Units are as follows: calcium, magnesium, potassium, sodium, mmol/24 h, creatinine, g/24 h[1] and mmol/24 h[2].

similar among the four groups (Table 4). Compared with the placebo group, blood pressure decreased significantly from baseline in the potassium group by 2.0 mm Hg for systolic pressure (95% confidence interval, −3.7 to −0.3), and by 1.7 mm Hg for diastolic pressure (−3.0 to −0.4). There were no significant changes in the magnesium or calcium groups. The combination of all three minerals had less effect on blood pressure than potassium and was not significantly different from placebo.

When the multiple regression analysis was used to adjust the blood pressure changes for baseline blood pressure and urinary excretion of the mineral or minerals that were supplemented, the differences were slightly diminished between treatment groups and the placebo group. These adjusted differences were for potassium −1.4 systolic ($P=.09$)/−1.3 diastolic ($P=.04$), for calcium −0.1 systolic ($P=.9$)/−0.4 diastolic ($P=.5$), for magnesium −0.5 systolic ($P=.5$)/−0.3 diastolic ($P=.6$), and for all three supplements −1.0 systolic ($P=.2$)/−0.8 diastolic ($P=.2$). Adding baseline sodium excretion to the multiple regression analysis did not affect the differences in blood pressure between the treatment groups and the placebo group. Subgroup analysis did not reveal differences in the blood pressure changes between participants who had baseline blood pressure levels, urinary cation excretion, urinary sodium excretion, or dietary cation intake above versus below the mean.

Blood pressure at baseline showed expected diurnal variation in the day-shift workers (Fig 1). This diurnal pattern was similar in all groups at baseline and during supplementation. The night-shift workers had a blunted diurnal variation (data not shown). The changes in blood pressure from baseline for 2-hour intervals were analyzed in each treatment group for the full group and the day-shift workers separately. There were not enough night-shift workers in each group for separate analysis of change (4 to 5 in each group except for 8 in the magnesium group). The results for the full group (Figs 2 and 3) and the day-shift workers were similar. The decrease in blood pressure in the potassium group was fairly uniform throughout the 24 hours of monitoring, except in the late evening when the hourly differences tended to be less than at other times (Figs 2 and 3). An effect of calcium, magnesium, or the combination of minerals on blood pressure was not apparent at any interval during the 24 hours.

There were no significant differences in the frequency of symptoms between the groups except for increased perception of energy level in the potassium group (8/49, 16%) compared with the control group (5/103, 5%), and loose stools in the magnesium group (20/50, 40%) compared with the control group (18/103, 17%). In each group, 1 to 2 participants withdrew from the study due to possible side effects. None were required to withdraw because of elevated blood pressure (>160 systolic or >95 diastolic).

Discussion

We determined that supplementation with potassium, but not with magnesium or calcium, significantly lowered blood pressure in a normotensive group of US nurses who reported low intakes of these minerals. Mean intakes of potassium, calcium, and magnesium in this trial corresponded to the 10th, 17th, and 10th percentiles of the Nurses Health Study II population. These mean intakes were also lower than the means for the US population of white women, ages 35 to 49 years, adjusted to the same total energy intake as the nurses: potassium 2433 versus 3077 mg,[34] calcium 638 versus 1059 mg,[34] and magnesium 239 versus 344 mg.[35] The overall nurse population had intake of these minerals that were similar to the means for the US population. The low reported intake in the nurses in this trial could be confirmed biochemically for potassium because of the close biological relationship between dietary intake and urinary excretion. Mean baseline 24-hour urinary excretion of potassium was 40 mmol, which corresponds to the reported daily intake of 62 mmol (2433 mg). Most other trials of

TABLE 4. Average 24-Hour Ambulatory Blood Pressures

Treatment	Change from Baseline				Average Change, Treatment vs Placebo
	Baseline	Midpoint	End	Average	
Potassium					
Systolic	118±8	−2.0±5.8	−1.5±5.2	−1.6±4.9	−2.0 (−3.7, −0.3), *P*=.02
Diastolic	75±7	−1.7±4.2	−1.4±3.8	−1.5±3.7	−1.7 (−3.0, −0.4), *P*=.01
n	49	49	46	49	
Calcium					
Systolic	117±9	−0.2±5.7	−0.3±6.3	−0.2±5.4	−0.6 (−2.2, 1.0), *P*=.27
Diastolic	74±6	−0.5±4.2	−0.6±3.8	−0.5±3.6	−0.7 (−2.0, 0.6), *P*=.23
n	53	53	51	53	
Magnesium					
Systolic	117±10	−0.7±5.8	−0.5±4.8	−0.5±4.9	−0.9 (−2.6, 0.8), *P*=.29
Diastolic	74±7	−0.5±4.5	−0.5±4.4	−0.4±4.1	−0.7 (−2.2, 0.8), *P*=.32
n	50	50	48	50	
K+Ca+Mg					
Systolic	116±7	−0.3±5.6	−1.8±5.5	−0.9±4.8	−1.3 (−3.0, 0.4), *P*=.13
Diastolic	73±6	−0.1±3.8	−1.4±3.9	−0.7±3.4	−0.9 (−2.2, 0.4), *P*=.17
n	45	45	43	45	
Placebo					
Systolic	115±8	0.3±5.3	0.4±5.6	0.4±4.8	...
Diastolic	73±6	0.2±4.0	0.3±4.8	0.2±3.9	...
n	103	103	102	103	

Values are mean±SD; 95% confidence intervals are in parentheses.

potassium supplementation were of women who had a higher urinary potassium excretion, 50 to 60 mmol.[29,36–39] Reported compliance was excellent for the potassium, calcium, and magnesium supplements, and it was confirmed by increases in urinary excretion of each supplement. Urinary creatinine excretion averaged 1.1 to 1.2 g/d, which is similar to other studies in women.[36,40] The molar ratio of dietary potassium to urinary potassium was 1.5 compared with 1.3 in a previous study,[41] also suggesting good compliance with urine collections. Finally, the quantitative relationship between changes in intake and urinary excretion of potassium demonstrated near perfect compliance in the two groups that received potassium. (Because the biological relationships between dietary and urinary calcium and magnesium are not quantitative, the significant increases in excretion during supplementation give qualititative confirmation of compliance.) Therefore, the trial achieved its goals for a low baseline mineral intake and adherence to the supplementation that were needed to test the hypotheses.

Potassium lowers blood pressure in hypertensives, −8.2/−4.5 mm Hg in one meta-analysis,[16] and −5.1/−3.0 mm Hg in another.[10] Potassium trials in hypertensive women[38] or those in which women comprised at least half of the group[23,37,39,42,43] showed blood pressure–lowering similar to studies in hypertensive men. In contrast, potassium supplementation had little or no effect on blood pressure in normotensive persons who were not selected for low intake, even with higher doses of potassium than used in the present study.[36,44,45] For example, in

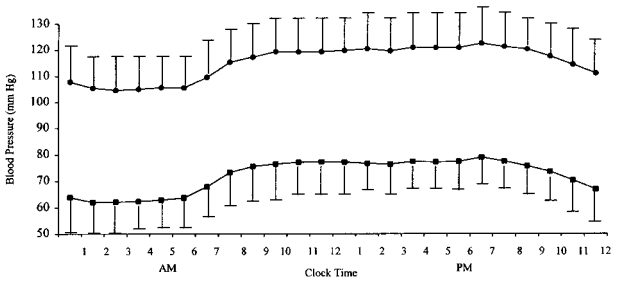

Figure 1. Ambulatory blood pressure at baseline for day-shift workers. n=274. Data points show means and standard deviations. ●, systolic; ■, diastolic.

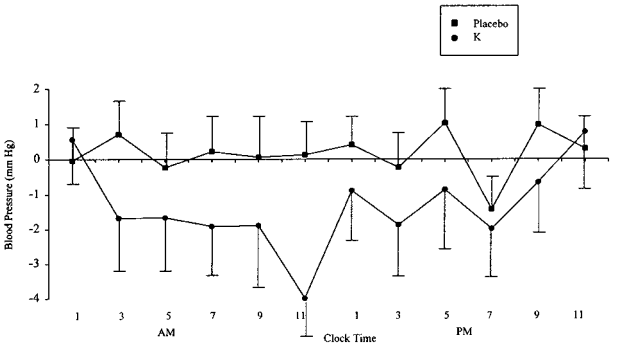

Figure 2. Diastolic blood pressure changes in the potassium and placebo groups. Ambulatory blood pressure measurements were averaged for 2-hour intervals with the data points indicating the median time within each 2-hour interval. ●, potassium group (n=49); ■, placebo group (n=103). Data points show the mean changes from baseline averaging the 8- and 16-week measurements during supplementation. Error bars show standard errors of the changes.

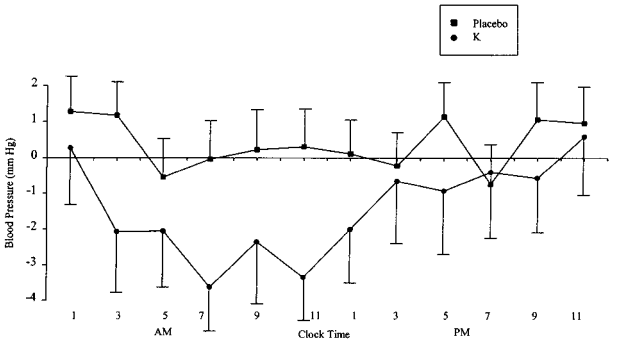

Figure 3. Systolic blood pressure changes in the potassium and placebo groups. See Fig 2 for description.

the Trials of Hypertension Prevention, Phase 1, potassium, 60 mmol, did not significantly lower blood pressure compared with placebo in the entire group of 353 normotensive persons, or in the 98 women.[36] Other trials in normotensive persons suggest that potassium supplementation has an enhanced effect on blood pressure in persons with low, rather than average or high, usual intake. Reducing potassium intake from an average to a very low level, 77 to 10 mmol, increased blood pressure significantly, by 6.1/3.6 mm Hg, whereas raising potassium intake from 62 to 90 mmol produced nonsignificant changes of −1.0/−3.2 mm Hg.[46] In blacks, raising potassium from a low level of 32 to 35 mmol to 112 to 115 mmol reduced blood pressure by 6.9/2.5 mm Hg.[47] However, hyper-responsiveness to potassium in blacks is an alternative explanation.[38,42,43,48] These studies, in combination with the present study, suggest that in normotensives, dietary potassium becomes important for blood pressure regulation at low intake.

In the present trial, neither magnesium nor calcium supplements lowered blood pressure. Two recent meta-analyses found no overall effects of calcium on blood pressure in normotensive persons.[17,18] In a recent trial in normotensive children, ages 10 to 13 years, systolic blood pressure–lowering was inversely proportional to the baseline calcium intake.[49] However, in adults with usual calcium intake less than 600 mg, calcium supplements did not lower blood pressure.[50–55] Therefore, we conclude that increasing calcium intake by supplementation does not lower blood pressure in normotensive adults with low or average baseline intake.

Several previous trials studied combinations of cations. Trials of low-fat milk, which raised primarily calcium but also produced mild increases in magnesium and potassium intakes, did not lower blood pressure in hypertensives (mean change, +4/+1 mm Hg)[51]; the effects in normotensives were significant for systolic pressure but not diastolic blood pressure (−2.7/+0.2 mm Hg).[56] In hypertensive patients, magnesium supplements did not augment the blood pressure–lowering effect of potassium.[23] In fact, the blood pressure reduction was slightly less with the combination than with potassium. In mildly hypertensive subjects, none of the combinations, potassium and magnesium, potassium and calcium, or magnesium and calcium significantly lowered blood pressure.[28] These results were surprising because the two combinations with potassium did not cause the decrease in blood pressure expected from potassium itself. This raises the possibility that magnesium and calcium, ineffective as single supplements, could actually interfere with the blood pressure–lowering action of potassium. The present study also suggests such a negative interaction, since the blood pressure decrease in the group that received the combination of potassium, calcium, and magnesium was smaller in magnitude than in the group that received potassium alone and was not significant. Epidemiological studies generally have found an inverse relationship between dietary calcium and blood pressure levels.[7,12,13] However, in certain populations, there is evidence that calcium may contribute to elevated blood pressure. In a population study, urinary calcium excretion was positively associated with blood pressure.[57] In the present and other studies,[28,30] calcium supplements raise urinary calcium excretion. Gruchow et al[58] found that potassium had an inverse association with blood pressure but only in persons whose calcium intakes were in the lower third of the US population. In those persons with average or high calcium intakes, potassium was not associated with low blood pressure.

The results of the present trial may be used to interpret findings from epidemiological studies that found associations of dietary intakes of calcium, magnesium, or potassium with hypertension or blood pressure levels.[1–15] It is difficult in multiple regression analysis to separate the individual effects of these minerals because the intakes are strongly correlated with each other. The magnitude of the blood pressure–lowering effect of potassium in the present trial is consistent with the difference in blood pressure seen from high to low potassium intake in these populations. In the large-scale Dietary Approaches to Stop Hypertension (DASH) trial,[59] a diet rich in fruits and vegetables that raised lower-than-average potassium and magnesium intakes significantly decreased 24-hour ambulatory blood pressures in persons with high-normal diastolic blood pressure or Stage 1 hypertension (−3.1/−2.1 mm Hg), and significantly decreased clinic blood pressures in the hypertensive group. The blood pressure–lowering in the DASH trial is consistent with the effects of potassium in the present and other supplementation trials. This comparison also suggests that potassium chloride, as used in the supplementation trials, has an effect on blood pressure similar to that of potassium in food, which is mainly in the form of other salts such as citrate. In conclusion, the present study points toward potassium, rather than magnesium or calcium, as the cause of lower blood pressures in populations and provides support for nutritional guidelines to increase dietary potassium to prevent hypertension.

Acknowledgments

We thank the dedicated nurses from the Nurses Health Study II who participated in this study. The study was supported by grants from the National Heart, Lung, and Blood Insitute, R01 HL34593, and the National Cancer Institute, R01 CA50385, and by a grant from the National Institutes of Health, NCRR GCRC M01 RR02635 to the Brigham and Women's Hospital General Clinical Research Center.

References

1. Reed D, McGee D, Yano K, Hankin J. Diet, blood pressure, and multicollinearity. *Hypertension*. 1985;7:405–410.
2. Joffres MR, Reed DM, Yano K. Relationship of magnesium intake and other dietary factors to blood pressure: the Honolulu Heart Study. *Am J Clin Nutr*. 1987;45:469–475.

3. Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *BMJ*. 1988;297:319–328.
4. Kesteloot H, Joossens JV. Relationship of dietary sodium, potassium, calcium, and magnesium with blood pressure: Belgian Interuniversity Research on Nutrition and Health. *Hypertension*. 1988;12:594–599.
5. Sacks FM, Kass EH. Low blood pressure in vegetarians: effects of specific foods and nutrients. *Am J Clin Nutr*. 1988;48:795–800.
6. Khaw K-T, Barrett-Connor E. The association between blood pressure, age, and dietary sodium and potassium: a population study. *Circulation*. 1988;77:53–61.
7. Witteman JC, Willett WC, Stampfer MJ, Colditz GA, Sacks FM, Speizer FE, Rosner B, Hennekens CH. A prospective study of nutritional factors and hypertension among US women. *Circulation*. 1989;80:1320–1327.
8. Iso H, Terao A, Kitamura A, Sato S, Naito Y, Kiyama M, Tanigaki M, Iida M, Konishi M, Shimamoto T, Komachi Y. Calcium intake and blood pressure in seven Japanese populations. *Am J Epidemiol*. 1991;133:776–783.
9. Ascherio A, Rimm EB, Giovannucci EL, Colditz GA, Rosner B, Willett WC, Sacks FM, Stampfer MJ. A prospective study of nutritional factors and hypertension among US men. *Circulation*. 1992;86:1475–1484.
10. Whelton PK. Potassium and blood pressure. In: Izzo JL, Black HR, eds. *Hypertension Primer. Council on High Blood Pressure Research*. Dallas, Tx: American Heart Association; 1993:170–172.
11. Simon JA, Obarzanek E, Daniels SR, Frederick MM. Dietary cation intake and blood pressure in black girls and white girls. *Am J Epidemiol*. 1994; 139:130–140.
12. Cappuccio FP, Elliott P, Allender PS, Follman DA, Cutler JA. Epidemiologic association between dietary calcium intake and blood pressure: a meta-analysis of published data. *Am J Epidemiol*. 1995;142:935–45.
13. Pryer J, Cappuccio FP, Elliott P. Dietary calcium and blood pressure: a review of the observational studies. *J Hum Hypertens*. 1995;9:597–604.
14. Ma J, Folsom AR, Melnick SL, Eckfeldt JH, Sharrett AR, Nabulsi AA, Hutchinson RG, Metcalf PA, for the Atherosclerosis Risk in Communities study group. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. *J Clin Epidemiol*. 1995;48:927–940.
15. Ascherio A, Hennekens CH, Willett WC, Sacks FM, Rosner B, Manson J, Witteman J, Stampfer MJ. A prospective study of nutritional factors, blood pressure, and hypertension among US women. *Hypertension*. 1996; 27:1065–72.
16. Cappuccio FP, MacGregor GA. Does potassium supplementation lower blood pressure? A meta-analysis of published trials. *J Hypertens*. 1991;9: 465–473.
17. Allender PS, Cutler JA, Follmann D, Cappuccio FP, Pryer J, Elliott P. Dietary calcium and blood pressure: a meta-analysis of randomized clinical trials. *Ann Intern Med*. 1996;124:825–831.
18. Bucher HC, Cook RJ, Guyatt GH, Lang JD, Cook DJ, Hatala R, Hunt DL. Effects of dietary calcium supplementation on blood pressure: a meta-analysis of randomized controlled trials. *JAMA*. 1996;275:1016–1022.
19. Cappuccio FP, Markandu ND, Beynon GW, Shore AC, Sampson B, MacGregor GA. Lack of effect of oral magnesium on high blood pressure: a double blind study. *BMJ*. 1985;291:235–238.
20. Henderson DG, Schierup J, Schodt T. Effect of magnesium supplementation on blood pressure and electrolyte concentrations in hypertensive patients receiving long term diuretic treatment. *BMJ*. 1986;293:664–665.
21. Motoyama T, Sano H, Fukuzaki H. Oral magnesium supplementation in patients with essential hypertension. *Hypertension*. 1989;13:227–232.
22. Zemel PC, Zemel MB, Urberg M, Douglas FL, Geiser R, Sowers JR. Metabolic and hemodynamic effects of magnesium supplementation in patients with essential hypertension. *Am J Clin Nutr*. 1990;51:665–669.
23. Patki PS, Singh J, Gokhale SV, Bulakh PM, Shrotri DS, Patwardhan B. Efficacy of potassium and magnesium in essential hypertension: a double blind, placebo controlled, crossover study. *BMJ*. 1990;301:521–523.
24. Lind L, Lithell H, Pollare T, Ljunghall S. Blood pressure response during long-term treatment with magnesium is dependent on magnesium status: a double-blind, placebo-controlled study in essential hypertension and in subjects with high-normal blood pressure. *Am J Hypertens*. 1991;4: 674–679.
25. Widman L, Wester PO, Stegmayr BK, Wirell M. The dose-dependent reduction in blood pressure through administration of magnesium: a double-blind placebo controlled cross-over study. *Am J Hypertens*. 1993;6: 41–45.
26. Wirell MP, Wester PO, Stegmayr BG. Nutritional dose of magnesium in hypertensive patients on beta blockers lowers systolic blood pressure: a double-blind, cross-over study. *J Intern Med*. 1994;236:189–195.
27. Witteman JC, Grobbee DE, Derkx FH, Bouillon R, de Bruijn AM, Hofman A. Reduction of blood pressure with oral magnesium supplementation in women with mild to moderate hypertension. *Am J Clin Nutr*. 1994;60:129–135.
28. Sacks FM, Brown LE, Appel L, Borhani NO, Evans D, Whelton P. Combinations of potassium, calcium, and magnesium supplements in hypertension. *Hypertension*. 1995;26:950–956.
29. The Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels: results of the Trials of Hypertension Prevention, Phase 1. *JAMA*. 1992;267:1213–1220.
30. Yamamoto ME, Applegate WB, Klag MJ, Borhani NO, Cohen JD, Kirchner KA, Lakatos E, Sacks FM, Taylor JO, Hennekens CH, for the TOHP Collaborative Research Group. Lack of blood pressure effect with calcium and magnesium supplementation in adults with high-normal blood pressure: results from Phase I of the Trials of Hypertension Prevention (TOHP). *Ann Epidemiol*. 1995;5:96–107.
31. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122:51–65.
32. Dunnett CW. A multiple comparison procedure for comparing several treatments with a control. *Am Stat Assoc J*. 1955;50:1096–1121.
33. SAS/STAT User's Guide, Release 6.03 Edition. Cary, NC: SAS Institute, Inc; 1988:1–1028.
34. Block G, Subar AF. Estimates of nutrient intake from a food frequency questinnaire: the 1987 National Health Interview Survey. *J Am Diet Assoc*. 1992;92:969–977.
35. Alaimo K, McDowell MA, Briefel RR, Bischof AM, Caughman CR, Loria CM, Johnson CL. *Dietary intake of vitamins, minerals, and fiber of persons ages 2 months and over in the United States*: Third National Health and Nutrition Examination Survey, Phase 1, 1988–91. Advance Data, 1994; 258:1–28.
36. Whelton PK, Buring J, Borhani NO, Cohen JD, Cook N, Cutler JA, Kiley JE, Kuller LH, Satterfield S, Sacks FM, Taylor JO, for the TOHP Collaborative Research Group. The effect of potassium supplementation in persons with a high-normal blood pressure: results from Phase I of the Trials of Hypertension Prevention (TOHP). *Ann Epidemiol*. 1995;5:85–95.
37. MacGregor GA, Smith SJ, Markandu ND, Banks RA, Sagnella GA. Moderate potassium supplementation in essential hypertension. *Lancet*. 1982;2:567–570.
38. Matlou SM, Isles CG, Higgs A, Milne FJ, Murray GD, Schultz E, Starke IF. Potassium supplementation in blacks with mild to moderate essential hypertension. *J Hypertens*. 1986;4:61–64.
39. Fotherby MD, Potter JF. Potassium supplementation reduces clinic and ambulatory blood pressure in elderly hypertensive patients. *J Hypertens*. 1992;10:1403–1408.
40. Joossens JV, Claessens J, Geboers J. Electrolytes and creatinine in multiple 24-hour urine collections (1970–1974). In: Kesteloot H, Joossens JV, eds. *Epidemiology of Arterial Blood Pressure*. The Hague, Martinus-Nijhoff; 1980: 45–63.
41. Kesteloot H, Joossens JV. The relationship between dietary intake and urinary excretion of sodium, potassium, calcium, and magnesium. *J Hum Hypertens*. 1990;4:527–33.
42. Kaplan NM, Carnegie A, Raskin P, Heller JA, Simmons M. Potassium supplementation in hypertensive patients with diuretic-induced hypokalemia. *N Engl J Med*. 1985;312:746–749.
43. Obel AO. Placebo-controlled trial of potassium supplements in black patients with mild essential hypertension. *J Cardiovasc Pharmacol*. 1989;14: 294–296.
44. Miller JZ, Weinberger MH, Christian JC. Blood pressure response to potassium supplementation in normotensive adults and children. *Hypertension*. 1987;10:437–442.
45. Grimm RH, Neaton JD, Elmer PJ, Svendsen KH, Levin J, Segal M, Holland L, Witte LF, Clearman DR, Kofron P, LaBounty RK, Crow R, Prineas RJ. The influence of oral potassium chloride on blood pressure in hypertensive men on a low sodium diet. *N Engl J Med*. 1990;322:569–574.
46. Krishna GG, Miller E, Kapoor S. Increased blood pressure during potassium depletion in normotensive men. *N Engl J Med*. 1989;320: 1177–1182.
47. Brancati FL, Appel LJ, Seidler AJ, Whelton PK. The effect of potassium supplementation on blood pressure in African Americans on a low potassium diet: a randomized double-blind placebo-controlled trial. *Arch Intern Med*. 1996;156:61–67.

48. Svetkey LP, Yarger WE, Feussner JR, DeLong E, Klotman PE. Double-blind, placebo-controlled trial of potassium chloride in the treatment of mild hypertension. *Hypertension*. 1987;9:444–450.
49. Gillman MW, Hood MY, Moore LL, Nguyen US, Singer MR, Andon MB. Effect of calcium supplementation on blood pressure in children. *J Pediatr*. 1995;127:186–192.
50. Tanji JL, Lew EY, Wong GY, Treguboff C, Ward JA, Amsterdam EA. Dietary calcium supplementation as a treatment for mild hypertension. *J Am Board Fam Pract*. 1991;4:145–150.
51. Kynast-Gales SA, Massey LK. Effects of dietary calcium from dairy products on ambulatory blood pressure in hypertensive men. *J Am Diet Assoc*. 1992;92:1497–1501.
52. Cappuccio FP, Markandu ND, Beynon GW, Shore AC, MacGregor GA. Effect of increasing calcium intake on urinary sodium excretion in normotensive subjects. *Clin Sci*. 1986;71:453–456.
53. van Beresteyn EC, Schaafsma G, de Waard H. Oral calcium and blood pressure: a controlled intervention trial. *Am J Clin Nutr*. 1986;44:883–888.
54. Siani A, Strazzullo P, Guglielmi S, Pacioni D, Giacco A, Iacone R, Mancini M. Controlled trial of low calcium versus high calcium intake in mild hypertension. *J Hypertens*. 1988;6:253–256.
55. Nowson C, Morgan T. Effect of calcium carbonate on blood pressure. *J Hypertens*. 1986;4(suppl 6):S673–S675.
56. van Beresteijn EC, van Schaik M, Schaafsma G. Milk: does it affect blood pressure? A controlled intervention study. *J Intern Med*. 1990;228:477–482.
57. Kesteloot H, Geboers J. Calcium and blood pressure. *Lancet*. 1982;1:813–815.
58. Gruchow HW, Sobocinski KA, Barboriak JJ. Calcium intake and the relationship of dietary sodium and potassium to blood pressure. *Am J Clin Nutr*. 1988;48:1463–1470.
59. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N, for the DASH Collaborative Research Group. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med*. 1997;336:1117–1124.