Effects of Potassium Chloride and Potassium Bicarbonate on Endothelial Function, Cardiovascular Risk Factors, and Bone Turnover in Mild Hypertensives

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Abstract—To determine the effects of potassium supplementation on endothelial function, cardiovascular risk factors, and bone turnover and to compare potassium chloride with potassium bicarbonate, we carried out a 12-week randomized, double-blind, placebo-controlled crossover trial in 42 individuals with untreated mildly raised blood pressure. Urinary potassium was 77±16, 122±25, and 125±27 mmol/24 hours after 4 weeks on placebo, potassium chloride, and potassium bicarbonate, respectively. There were no significant differences in office blood pressure among the 3 treatment periods, and only 24-hour and daytime systolic blood pressures were slightly lower with potassium chloride. Compared with placebo, both potassium chloride and potassium bicarbonate significantly improved endothelial function as measured by brachial artery flow-mediated dilatation, increased arterial compliance as assessed by carotid-femoral pulse wave velocity, decreased left ventricular mass, and improved left ventricular diastolic function. There was no significant difference between the 2 potassium salts in these measurements. The study also showed that potassium chloride reduced 24-hour urinary albumin and albumin:creatinine ratio, and potassium bicarbonate decreased 24-hour urinary calcium, calcium:creatinine ratio, and plasma C-terminal cross-linking telopeptide of type 1 collagen significantly. These results demonstrated that an increase in potassium intake had beneficial effects on the cardiovascular system, and potassium bicarbonate may improve bone health. Importantly, these effects were found in individuals who already had a relatively low-salt and high-potassium intake. **(*Hypertension*. 2010;55:681-688.)**

Key Words: potassium chloride ■ potassium bicarbonate ■ endothelial function ■ cardiovascular risk factors ■ bone turnover ■ randomized trial

Many randomized trials have shown that an increase in potassium intake lowers blood pressure (BP), particularly in individuals with raised BP.[1] Increasing evidence also suggests that a higher potassium intake may have beneficial effects on endothelial function, renal disease, arterial compliance, left ventricular (LV) mass and function, and bone mineral density.[2] The evidence for many of these effects is mainly from experimental studies in animals, and few well-controlled trials have studied such effects in humans.

Most previous studies on potassium have used potassium chloride, which is convenient for making the study double blinded by using slow-release potassium chloride versus slow-release potassium chloride placebo.[1] These studies have demonstrated clear benefits of potassium chloride, particularly on BP. Increasing potassium intake has been recommended as an important approach to lowering BP not only in individuals with raised BP but also in those with normal BP. However, no one is suggesting that the whole population take potassium chloride supplements. The best way to increase potassium intake is to increase the consumption of foods that are high in potassium, for example, fruit and vegetables. Potassium in fruit and vegetables is not in the form of potassium chloride, but a mixture of potassium phosphate, sulfate, citrate, and many organic anions, including proteins, most of which are precursors of potassium bicarbonate.[3] It is unclear whether potassium bicarbonate has a greater or lesser effect on BP and other cardiovascular risk factors compared with potassium chloride. Potassium bicarbonate is known to increase calcium absorption when on a low-protein diet,[4] and bicarbonate has been shown to decrease N-telopeptide and calcium excretion in older individuals.[5]

We carried out a randomized, double-blind trial to determine the effects of an increase in potassium intake on endothelial function, BP, pulse wave velocity, LV mass and diastolic function, 24-hour urinary albumin and calcium excretion, and biochemical markers of bone turnover. In

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addition, our study aimed to compare potassium chloride with potassium bicarbonate, looking at whether there was a difference in their effects on these measurements.

Methods

Participants

Individuals aged 18 to 75 years, with sitting systolic BP of 140 to 170 mm Hg or diastolic BP of 90 to 105 mm Hg and with no previous treatment for raised BP, were eligible for the study. Exclusion criteria were impaired renal function with plasma creatinine >150 μmol/L, any secondary cause of hypertension, chronic diarrhea, history of ulcer disease, baseline plasma potassium >5.0 mmol/L, previous stroke, ischemic heart disease, heart failure, diabetes mellitus, malignancy, or liver disease. Women who were pregnant, breastfeeding, or on oral contraceptive pills were also excluded.

Participants were recruited from the Blood Pressure Unit clinic and from general practices in south London. The study was approved by the Wandsworth Local Research Ethics Committee. Written consent was obtained from all of the participants.

Study Design

The study was designed as a randomized, double-blind crossover trial. Participants were advised to keep their usual diet and lifestyle and to avoid intense physical exercise throughout the study. Randomization was carried out using computer-generated random numbers, by an independent company, Arkopharma, who supplied the study capsules but had no involvement in the conduct of the trial. Participants were allocated in random order to take 10 placebo capsules per day for 4 weeks, 10 potassium bicarbonate capsules per day (potassium: 6.4 mmol per capsule) for 4 weeks, or 10 potassium chloride capsules per day (potassium: 6.4 mmol per capsule) for 4 weeks. All of the participants and research staff were unaware of the treatment allocation.

Measurements

All of the measurements were taken at baseline (ie, before randomization) and at the end of each 4-week randomized period. BP and 24-hour ambulatory BP monitoring were recorded as described previously.[6] Blood samples were collected, after an overnight fast, for routine biochemistry, plasma renin activity, aldosterone, and biochemical markers of bone turnover, including procollagen type I N-terminal propeptide, bone-specific alkaline phosphatase, osteocalcin, and C-terminal cross-linking telopeptide of type 1 collagen (βCTX). Plasma procollagen type I N-terminal propeptide, βCTX, and osteocalcin were measured using an electrochemiluminescent immunoassay on an E module immunoanalyzer (Roche) and bone-specific alkaline phosphatase by a commercial immunometric assay (Metra Biosystems). Interassay coefficient of variation was as follows: procollagen type I N-terminal propeptide <4%; βCTX <5%; osteocalcin <8%; and bone-specific alkaline phosphatase <8%. Two consecutive 24-hour urine samples were collected on the last 2 days of each study period for measurements of urinary electrolytes, creatinine, and albumin excretion. Urinary albumin was measured by laser immunonephelometry and high-sensitivity ELISA, as described previously.[6] The mean of two 24-hour urinary measurements was used in the analysis. One 2-hour early morning fasted urine sample was collected for measurements of free pyridinoline and free deoxypyridinoline. A modification of the high-performance liquid chromatography method[7] was used to measure these cross-links (interassay coefficient of variation: <5.5% for both).[8] Results were expressed relative to creatinine.

Endothelial function was assessed by noninvasive technique of brachial artery flow-mediated dilatation (endothelium dependent) and after glyceryl trinitrate stimuli (endothelium independent). The brachial artery was scanned according to an established protocol.[9] A tourniquet was located at the right proximal forearm and inflated to a pressure of 300 mm Hg for 4.5 minutes. Brachial artery dilatation was measured for 5 minutes after tourniquet release. After 10 to 15 minutes of rest, sublingual glyceryl trinitrate spray (400 μg) was administered, and images were continuously recorded for an additional 5 minutes. This technique was validated to measure flow-mediated dilatation as a marker of endothelial function, with a mean day-to-day variability of 0.90±0.48%.[9]

Carotid-femoral pulse wave velocity was measured noninvasively using an automatic device (Complior) as described previously and validated.[6,10] Transthoracic echocardiography examination was performed using a Vivid 7 ultrasound scanner and a 2.5-Mhz probe (General Electric-GE Vingmed). LV internal dimensions at end diastole and end systole were measured on parasternal long-axis M-mode images. Ejection fraction, LV mass, and LV mass index were calculated.[11] Diastolic function was assessed by measurements of mitral and pulmonary vein flow, tissue Doppler, and color M-mode flow propagation. Transmitral flow velocities were obtained from the apical 4-chamber view using a pulsed-wave Doppler positioned at the tip of the leaflets. In the presence of a pseudonormal filling pattern, measurements were done during the Valsalva maneuver. Peak E wave (early diastolic), A wave (atrial), E deceleration, A wave duration, and isovolumic relaxation time were measured. E prime tissue Doppler velocity was acquired in apical view by placing a sample volume on a lateral mitral annulus. Systolic, diastolic, and atrial reversal pulmonary vein flow velocities were obtained by placing pulsed-wave Doppler within the right upper vein. All of the measurements were performed in accordance with the American Society of Echocardiography recommendations.

Table 1. Baseline Characteristics

Variable	Mean	SD
Age, y	51	10
BMI, kg/m^2	29.7	4.8
Office BP and pulse rate		
SBP, mm Hg	145	11
DBP, mm Hg	91	7
Pulse rate, bpm	65	8
Ambulatory BP, mm Hg		
24-hour SBP	140	8
24-hour DBP	87	8
Day SBP	147	8
Day DBP	92	8
Night SBP	133	9
Night DBP	81	8
24-h urinary measurements		
Volume, mL/24 h	1702	758
Sodium, mmol/24 h	122	38
Potassium, mmol/24 h	80	21
Creatinine, mmol/24 h	15.0	3.8
Plasma measurements		
Sodium, mmol/L	140	2
Potassium, mmol/L	4.4	0.3
Creatinine, μmol/L	86	14
Renin activity, ng/mL/h*	0.17	0.10 to 0.38
Aldosterone, pmol/L	360	151

All of the values are expressed as mean and SD unless otherwise specified.
BMI indicates body mass index; SBP, systolic BP; DBP, diastolic BP.
*Values are median and interquartile range.

Statistical Analysis

For normally distributed variables, repeated-measures ANOVA was performed to examine whether there was a significant difference among 3 treatment regimens. Where significant difference was

Table 2. Changes in BP, Biochemistry, 24-h Urinary Albumin Excretion, Pulse Wave Velocity, and Vascular Function During the Randomized Crossover Phase

Variable	Placebo	Potassium Chloride	Potassium Bicarbonate	*P*
Office BP and pulse rate				
SBP, mm Hg	145 (15)	142 (11)	144 (13)	0.344
DBP, mm Hg	91 (9)	90 (9)	90 (9)	0.261
Pulse pressure, mm Hg	54 (13)	52 (9)	54 (11)	0.284
Pulse rate, bpm	65 (8)	65 (9)	65 (9)	0.747
Ambulatory BP, mm Hg				
24-h SBP	142 (10)	139 (9)	142 (11)#	0.043
24-h DBP	88 (9)	87 (8)	89 (9)	0.162
Day SBP	148 (10)	146 (10)	149 (11)‖	0.019
Day DBP	93 (11)	92 (10)	95 (10)	0.078
Night SBP	135 (11)	133 (10)	135 (12)	0.361
Night DBP	82 (9)	81 (9)	82 (10)	0.501
Body weight, kg	87.9 (14.4)	87.9 (14.3)	88.1 (14.5)	0.216
24-h urinary measurements				
Volume, mL/24 h	1650 (582)	1675 (667)	1580 (557)	0.430
Sodium, mmol/24 h	127 (44)	134 (49)	129 (45)	0.672
Potassium, mmol/24 h	77 (16)	122 (25)§	125 (27)§	<0.001
Creatinine, mmol/24 h	14.7 (3.3)	14.4 (3.9)	14.8 (3.5)	0.533
Albumin, mg/24 h*	10.4 (6.0 to 19.1)	7.9 (5.3 to 12.5)†	10.9 (5.8 to 16.8)¶	0.001
Albumin:creatinine ratio, mg/mmol*	0.72 (0.48 to 1.09)	0.57 (0.40 to 0.99)†	0.69 (0.51 to 1.04)‖	0.005
Plasma measurements				
Sodium, mmol/L	139 (2)	139 (2)	139 (2)	0.822
Potassium, mmol/L	4.4 (0.3)	4.6 (0.2)‡	4.4 (0.3)	0.003
Chloride, mmol/L	104 (2)	104 (2)	104 (3)	0.326
Bicarbonate, mmol/L	28 (2)	28 (2)	28 (2)	0.643
Creatinine, μmol/L	85 (12)	85 (13)	86 (13)	0.659
Albumin, g/L	41 (3)	41 (4)	41 (4)	0.320
Renin activity, ng/mL/h*	0.12 (0.10 to 0.34)	0.17 (0.10 to 0.32)	0.17 (0.10 to 0.43)	0.507
Aldosterone, pmol/L	353 (165)	387 (152)	371 (141)	0.310
Hematocrit	0.43 (0.04)	0.42 (0.04)	0.43 (0.04)	0.162
Pulse wave velocity, m/s	11.6 (1.9)	10.8 (1.7)§	11.1 (2.0)†	<0.001
Brachial artery dilatation				
Brachial artery diameter, mm	4.78 (0.87)	4.79 (0.92)	4.73 (0.95)	0.719
Increase in diameter after FMD, %	3.13 (2.46)	5.81 (4.33)§	4.62 (2.90)‡	<0.001
Increase in diameter after GTN, %	10.22 (5.89)	10.08 (5.48)	10.84 (6.70)	0.536

All values are expressed as mean (SD) unless otherwise specified. FMD indicates flow-mediated dilatation; GTN, glyceryl trinitrate; SBP, systolic BP; DBP, diastolic BP.

*Values are median (interquartile range).

†$P<0.05$ vs placebo.

‡$P<0.01$ vs placebo.

§$P<0.001$ vs placebo.

‖$P<0.01$ vs potassium chloride.

¶$P<0.001$ vs potassium chloride.

#$P=0.057$ vs potassium chloride.

found, paired comparison was carried out using a paired *t* test. Bonferroni adjustment was made for multiple comparisons. The potential carryover effect was assessed using a general linear model. Because there was no significant carryover effect in any of the outcome measures, this factor was, therefore, not included in the model. For variables that were not normally distributed (eg, plasma renin activity and 24-hour urinary albumin), Friedman test was used for comparisons among 3 study periods, and Wilcoxon signed-ranks test was used for paired comparisons. A 2-tailed *P* value of <0.05 was regarded as significant. All of the statistical analyses were performed using SPSS.

Results

A total of 46 individuals agreed to take part in the study. Forty two (30 men and 12 women) completed the study and

Table 3. Changes in LV Geometry and Function During the Randomized Crossover Phase

Variable	Placebo	Potassium Chloride	Potassium Bicarbonate	*P*
LV geometry				
LV end diastolic diameter, cm	5.03 (0.54)	5.01 (0.57)	5.00 (0.55)	0.864
LV end systolic diameter, cm	3.26 (0.63)	3.22 (0.64)	3.23 (0.67)	0.649
Interventricular septal thickness at end diastole, cm	1.00 (0.17)	0.96 (0.15)†	0.98 (0.15)	0.017
LV posterior wall thickness at end diastole, cm	0.91 (0.18)	0.89 (0.19)	0.87 (0.17)†	0.006
LV mass, g	175.7 (48.1)	167.7 (48.3)*	166.7 (45.7)§	0.016
LV mass index, g/m^2	85.14 (21.83)	81.63 (22.23)*	81.11 (21.30)	0.035
LV systolic function				
Ejection fraction, %	64.66 (11.33)	65.83 (11.96)	66.13 (11.73)	0.225
Fractional shortening, %	35.24 (7.87)	36.31 (8.89)	36.56 (8.50)	0.118
LV diastolic function				
Peak E, m/s	0.63 (0.15)	0.68 (0.15)	0.71 (0.13)†	0.002
Peak A, m/s	0.68 (0.12)	0.63 (0.12)†	0.64 (0.13)*	0.001
E/A ratio	0.95 (0.29)	1.12 (0.28)‡	1.15 (0.31)‡	<0.001
Tissue Doppler imaging lateral wall E velocity (E′), m/s	0.078 (0.020)	0.077 (0.023)	0.080 (0.023)	0.681
E/E′	8.55 (2.98)	10.76 (9.97)	9.55 (3.23)	0.249
E-wave deceleration time, ms	189.8 (47.6)	174.0 (35.9)	172.8 (48.2)	0.058
A-wave duration, ms	124.5 (16.8)	117.3 (18.9)	116.1 (15.4)*	0.019
Isovolumic relaxation time, ms	83.0 (19.1)	77.6 (19.6)	75.9 (17.0)	0.074
LV flow propagation velocity, cm/s	42.74 (10.84)	49.80 (10.95)‡	48.33 (12.61)‡	<0.001
Peak systolic forward flow in pulmonary veins, m/s	0.57 (0.12)	0.54 (0.14)	0.54 (0.14)	0.069
Diastolic forward flow in pulmonary veins, m/s	0.38 (0.10)	0.44 (0.12)†	0.43 (0.12)†	<0.001
Pulmonary venous atrial reversal flow, m/s	0.29 (0.05)	0.26 (0.05)†	0.25 (0.05)‡	<0.001

*$P<0.05$ vs placebo.
†$P<0.01$ vs placebo.
‡$P<0.001$ vs placebo.
§$P=0.051$ vs placebo.

4 withdrew. The results reported here are based on the 42 participants who completed the study. There were 29 whites, 10 blacks, and 3 Asians. Other baseline characteristics are summarized in Table 1.

During the randomized crossover phase, the mean urinary potassium was 77±16 mmol/24 hours on placebo, 122±25 mmol/24 hours on potassium chloride, and 125±27 mmol/24 hours on potassium bicarbonate. There was, therefore, an increase of 45 mmol in 24-hour urinary potassium excretion with potassium chloride and 48 mmol with potassium bicarbonate compared with placebo. There was no significant difference in 24-hour urinary potassium between potassium chloride and potassium bicarbonate.

Compared with placebo, there was no significant change in office BP with either potassium chloride or potassium bicarbonate. Office BP was 145±15/91±9 mm Hg on placebo, 142±11/90±9 mm Hg on potassium chloride, and 144±13/90±9 mm Hg on potassium bicarbonate. Ambulatory BP monitoring showed that there was a small but significant difference in 24-hour and daytime systolic BPs among the 3 treatment periods. Paired comparison showed that 24-hour and daytime systolic BPs were slightly lower with potassium chloride when compared with potassium bicarbonate ($P=0.057$ for 24-hour systolic and $P<0.01$ for daytime systolic BPs; Table 2). Heart rate and body weight did not change with either potassium chloride or potassium bicarbonate.

Plasma potassium was 4.4±0.3 mmol/L on placebo; it was slightly higher on potassium chloride, that is, 4.6±0.2 mmol/L ($P<0.01$ compared with placebo); however, with potassium bicarbonate, mean plasma potassium was the same as that on placebo. There were no significant differences among the 3 treatment periods in hematocrit or plasma sodium, chloride, bicarbonate, creatinine, albumin, renin activity and aldosterone, or 24-hour urinary sodium and creatinine (Table 2).

Brachial artery diameter was similar among the 3 treatment periods. After flow-mediated dilatation, the increase in brachial artery diameter was significantly greater with both potassium chloride and potassium bicarbonate compared with

Table 4. Changes in Bone Metabolism Markers and Urinary Calcium and pH During the Randomized Crossover Phase

Variable	Placebo	Potassium Chloride	Potassium Bicarbonate	*P*
Plasma measurements				
P1NP, μg/L	39 (13)	40 (15)	39 (12)	0.900
Bone ALP, U/L	22 (8)	23 (9)	22 (8)	0.350
OC, μg/L	18.8 (5.2)	18.5 (5.7)	19.0 (5.4)	0.352
βCTX, μg/L	0.35 (0.13)	0.34 (0.14)	0.32 (0.11)†§	0.001
Second early morning fasting urine				
fPYD:creatinine ratio, nmol/mmol	16.1 (5.0)	15.9 (5.1)	15.8 (4.9)	0.640
fDPD:creatinine ratio, nmol/mmol	4.5 (1.5)	4.4 (1.5)	4.4 (1.4)	0.557
fPYD:fDPD ratio	3.6 (0.5)	3.6 (0.5)	3.7 (0.5)	0.951
24-h urine				
Calcium, mmol/24 h	4.4 (2.2)	4.3 (2.3)	3.7 (1.8)*	0.009
Calcium:creatinine ratio	0.31 (0.14)	0.31 (0.18)	0.26 (0.13)†§	0.002
pH	6.42 (0.58)	6.34 (0.65)	7.30 (0.53)‡‖	<0.001

P1NP indicates procollagen type I N-terminal propeptide; BAP, bone-specific alkaline phosphatase; fPYD, free pyridinoline; fDPD, free deoxypyridinoline; OC, osteocalcin.

*$P<0.05$ vs placebo.

†$P<0.01$ vs placebo.

‡$P<0.001$ vs placebo.

§$P<0.05$ vs potassium chloride.

‖$P<0.001$ vs potassium chloride.

placebo, but it was not significantly different between the 2 potassium salts. After glyceryl trinitrate, the increase in brachial artery diameter was similar among the 3 periods (Table 2). Pulse wave velocity showed a significant decrease with both potassium chloride and potassium bicarbonate compared with placebo, but there was no significant difference between the 2 potassium periods (Table 2).

The median 24-hour urinary albumin was 10.4 mg (interquartile range: 6.0 to 19.1 mg) on placebo and 7.9 mg (5.3 to 12.5 mg) on potassium chloride ($P<0.05$ compared with placebo and $P<0.001$ compared with potassium bicarbonate) and 10.9 mg (5.8 to 16.8 mg) on potassium bicarbonate. Compared with placebo, there was a 24% decrease in albumin excretion with potassium chloride; however, there was no significant change in albumin excretion with potassium bicarbonate. Urinary albumin:creatinine ratio was also significantly lower with potassium chloride compared with placebo and potassium bicarbonate (Table 2).

Echocardiographic data showed a small but significant difference in LV mass and LV mass index among the 3 treatment periods. Paired comparison showed that, compared with placebo, LV mass was significantly lower with potassium chloride ($P<0.05$) and borderline significant with potassium bicarbonate ($P=0.051$), and LV mass index was significantly lower with potassium chloride. LV systolic function did not show any significant change with either potassium salt. However, LV diastolic function was improved significantly with both potassium salts. This was shown by an increased E/A ratio, an increased diastolic forward flow in pulmonary veins, a decreased pulmonary venous atrial reversal flow, and an increased flow propagation velocity (Table 3). There was no significant difference between potassium chloride and potassium bicarbonate in any of the echocardiographic measurements (Table 3).

Table 4 shows 24-hour urinary calcium excretion and biochemical markers of bone turnover. There was a significant reduction in 24-hour urinary calcium, calcium:creatinine ratio, and plasma βCTX with potassium bicarbonate compared with placebo or potassium chloride; however, there was no significant change in other bone markers. Potassium chloride did not result in a significant change in urinary calcium or any markers of bone turnover compared with placebo. Urinary pH was significantly higher on potassium bicarbonate compared with placebo and potassium chloride (Table 4).

Discussion

Our study, for the first time, demonstrated that, in individuals with mildly raised BP who were already on a relatively low-salt and high-potassium intake, both potassium chloride and potassium bicarbonate significantly improved endothelial function, increased large elastic artery compliance, reduced LV mass, and improved LV diastolic function. In addition, potassium chloride reduced 24-hour urinary albumin, and potassium bicarbonate decreased 24-hour urinary calcium, calcium:creatinine ratio, and plasma βCTX, a marker of bone resorption. These results indicate that an increase in potassium intake has beneficial effects on the cardiovascular system and bone health. The 2 potassium salts appear to have a similar effect on most of the cardiovascular parameters studied; however, there are differences between them in the effects on calcium and bone metabolism and urinary albumin excretion.

In our study, there was no significant change in office BP with either potassium salt, and only 24-hour and daytime systolic BPs were slightly lower with potassium chloride. One study in stroke-prone spontaneously hypertensive rats

fed a low-normal–salt diet showed an increase in BP with potassium chloride but not with potassium bicarbonate.[12] However, many previous clinical trials demonstrated that potassium chloride lowered BP,[1] and limited data also suggested that nonchloride salts of potassium lowered BP to a similar extent as potassium chloride.[3,13] The discrepant findings between our study and other trials may be, at least, partially because of differences in baseline salt and potassium intake (ie, 122 and 80 mmol in our study compared with an average of ≈150 and 60 mmol, respectively in others[1]), as it has been documented that the effects of potassium on BP were attenuated with a lower salt[1,14] and higher potassium intake. In addition, our study may be underpowered to detect a small change in BP. Meta-analysis of randomized trials showed that potassium supplementation reduced BP by 4.4/2.5 mm Hg in hypertensives and 1.8/1.0 mm Hg in normotensives.[1] Furthermore, the decrease in BP was related to baseline BP, that is, the higher the baseline BP, the greater the decrease in BP with potassium supplementation.[15] Our study included participants with only mildly raised BP, and, thus, the effects of potassium on BP, if anything, would be smaller than those observed in previous trials in hypertensives. Our study had a power of only 50% to detect such a small change.

An increase in potassium intake has been shown to augment endothelium-dependent relaxation and preserve endothelial function through increased endothelial NO production in salt-loaded, Dahl salt-sensitive rats.[16] Using cultured bovine aortic endothelial cells, Oberleithner et al[17] showed that an increase in potassium concentration in the culture medium, within the physiological range, softened vascular endothelium and increased NO release. One small study in a group of salt-sensitive individuals on a high-salt intake showed that potassium supplementation for 1 week increased plasma and urinary NO levels.[18] A recent randomized trial in 117 hypertensives who were on a low fruit and vegetable intake (1 portion per day) showed that an increase in the consumption of fruit and vegetables improved endothelial function as assessed by forearm blood flow responses to acetylcholine in a dose-response manner.[19] Our findings are of considerable interest in that the effect of potassium on endothelial function was found in individuals on a relatively low-salt and high-potassium intake.

Pulse wave velocity is a measure of arterial distensibility. Epidemiological studies have shown that aortic pulse wave velocity is a strong independent predictor of future cardiovascular events.[20] Our finding of an improvement of large elastic artery compliance would suggest a potential beneficial effect of potassium on the cardiovascular system in the long term. Studies in Dahl salt-sensitive rats demonstrated that potassium supplementation enhanced aortic compliance[21] and protected against the development of vascular damage induced by salt loading, possibly through suppression of salt-induced oxidative stress.[22]

Urinary albumin excretion has been shown to be an important, independent, and continuous risk factor for the development and progression of renal disease and also for cardiovascular disease.[23] Experimental studies in hypertensive Dahl salt-sensitive rats demonstrated that both potassium chloride and potassium citrate prevented the development of renal vascular, glomerular, and tubular damage.[24] In humans, it was reported that chronic hypokalemia was related to renal lesions, for example, hypertrophy in the proximal tubules.[25] Our study showed that supplementation of potassium chloride reduced 24-hour urinary albumin, but potassium bicarbonate did not have such an effect. It is possible that the decrease in urinary albumin was because of the fall in 24-hour systolic BP, which occurred with potassium chloride.

Both LV mass and function are important independent predictors of cardiovascular morbidity and mortality. Experimental studies in dogs,[26] mice,[27] and human healthy volunteers[28,29] showed that hypokalemia induced LV hypertrophy and impaired LV function. Correction of hypokalemia by potassium supplementation prevented these adverse effects. These experiments clearly indicate that potassium has a significant effect on the structure and mechanical function of the heart. However, these studies were conducted under extreme conditions, for example, potassium depletion induced by diuretics followed by potassium repletion. Our study, on the contrary, was carried out under physiological conditions and demonstrated that an increase in potassium intake had a small but significant effect on LV mass and diastolic function. Other studies have shown that, in various cardiac diseases, for example, hypertensive heart disease, diastolic function is impaired before systolic function is affected. It is, therefore, possible that a higher potassium intake could preserve diastolic function at an early stage and prevent the development of heart disease in the long term.

A number of studies have shown that alkaline salt of potassium[30,31] reduced urinary calcium excretion and bone turnover in postmenopausal women. Our findings that potassium bicarbonate reduces urinary calcium and plasma βCTX are consistent with these observations. Our study also showed that potassium bicarbonate increased urinary pH and potassium chloride had no significant effect on urinary calcium but caused a small nonsignificant decrease in urinary pH. Because acid-base homeostasis also influences urinary calcium excretion, from our study it is difficult to know whether the effect of potassium bicarbonate on urinary calcium was attributable to a direct effect of potassium or through its effect on acid-base balance. A recent study in elderly individuals indicated that it was bicarbonate that had a favorable effect on calcium excretion and bone resorption.[5] However, a series of studies by Lemann et al[32] suggested that potassium had a direct effect on urinary calcium excretion, but by giving potassium as a citrate or bicarbonate salt, there was a greater effect compared with potassium chloride.

Longer-term trials on potassium and bone mineral density have shown inconsistent results. A study in postmenopausal women with osteopenia showed that supplementation of potassium citrate (30 mmol/d) for 1 year significantly increased lumbar spine bone mineral density.[33] However, a recent study in healthy postmenopausal women showed that potassium citrate at a dose of 18.5 or 55.5 mmol/d over 2 years had no significant effect on spine or hip bone mineral density despite a transient reduction in 24-hour urinary calcium and fasting urinary free deoxypyridinoline:creatinine ratio at 4 to 6 weeks.[34] A number of cross-sectional studies

have consistently shown that a higher potassium intake was associated with a higher bone mass.[35,36]

Perspectives

Our study demonstrated that, in individuals who already had a relatively low salt and high potassium intake, supplementation of either potassium chloride or potassium bicarbonate improved endothelial function and reduced cardiovascular risk factors. Potassium bicarbonate also had beneficial effects on calcium and bone metabolism. The potassium intake achieved in our study is very similar to the adequate intake for adults recommended by the US Institute of Medicine (120 mmol/d).[37] The current potassium intake in most populations is ≈60 to 70 mmol/d. Increasing potassium intake could play an important role in the prevention of cardiovascular disease and osteoporosis in the long term. Although our study was carried out in individuals with raised BP, it is likely that the general population would also benefit from an increase in potassium intake. This is reinforced by the findings from prospective studies in general populations that a higher potassium intake was related to a lower risk of cardiovascular disease.[38–41] A randomized trial in 1981 elderly Taiwanese demonstrated that replacing the usual salt for a potassium-enriched salt, with a subsequent increase of 76% in potassium intake and a 17% reduction in salt intake, resulted in a 40% reduction in cardiovascular disease mortality.[42] Our study provides further support for an increase in population potassium intake, and this would best be done by an increase in the consumption of foods high in potassium, for example, fruit and vegetables that in themselves have beneficial effects on health independent of potassium intake.

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Disclosures

None.

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