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. 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 (CTX). Plasma procollagen type I N-terminal propeptide, βCTX, and osteocalcin were measured using an electrochemiluminescent immunoassay on an E module immunanalyzer (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. 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, looking at whether there was a difference in their effects on these measurements.

**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 administered, and images were continuously recorded for an additional 5 minutes. This technique was validated to measure flow-mediated dilation as a marker of endothelial function, with a mean day-to-day variability of 0.90±0.48%. Carotid-femoral pulse wave velocity was measured noninvasively using an automatic device (Complior) as described previously and validated. 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. 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.
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. Fortytwo (30 men and 12 women) completed the study and
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 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/m²           | 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| 83.9 (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.
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 10.9 mg) on potassium chloride and potassium bicarbonate (Table 2). Urinary albumin:creatinine ratio was also significantly lower with potassium chloride 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).

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 \( \beta \)CTX 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 \( \beta \)CTX, 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.
fied a low-normal–salt diet showed an increase in BP with potassium chloride but not with potassium bicarbonate. However, many previous clinical trials demonstrated that potassium chloride lowered BP, and limited data also suggested that nonchloride salts of potassium lowered BP to a similar extent as potassium chloride. 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), as it has been documented that the effects of potassium on BP were attenuated with a lower salt 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. 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. 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. Using cultured bovine aortic endothelial cells, Oberleithner et al 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. 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. 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. 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 and protected against the development of vascular damage induced by salt loading, possibly through suppression of salt-induced oxidative stress. 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. Experimental studies in hypertensive Dahl salt-sensitive rats demonstrated that both potassium chloride and potassium citrate prevented the development of
have consistently shown that a higher potassium intake was associated with a higher bone mass.\textsuperscript{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).\textsuperscript{37} The current potassium intake in most populations is about 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.\textsuperscript{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.\textsuperscript{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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