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Potassium Citrate Prevents Increased Urine Calcium Excretion and Bone Resorption Induced by a High Sodium Chloride Diet

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The amount of sodium chloride in the diet of industrialized nations far exceeds physiological requirements. The impact of abundant dietary salt on skeletal health has yet to be established, but is potentially detrimental through increased urinary calcium losses. We examined the effect of increased dietary sodium chloride on urine calcium excretion and bone turnover markers in postmenopausal women and, further, whether potassium citrate attenuates the effects of increased dietary salt. Postmenopausal women (n = 60) were adapted to a low-salt (87 mmol/d sodium) diet for 3 wk, then randomized to a high-salt (225 mmol/d sodium) diet plus potassium citrate (90 mmol/d) or a high-salt diet plus placebo for 4 wk. Urine calcium, urine N-telopeptide, urine cAMP, serum osteocalcin, and fasting serum PTH were measured at the end of the low- and high-salt diets. On the high salt plus placebo diet, urine calcium increased 42 ± 12 mg/d (mean ± SEM), but decreased 8 ± 14 mg/d in the high salt plus potassium citrate group (P = 0.008, potassium citrate *vs.* placebo, unpaired t test). N-telopeptide increased 6.4 ± 1.4 nanomoles bone collagen equivalents per millimole creatinine in the high salt plus placebo group and 2.0 ± 1.7 nanomoles bone collagen equivalents per millimole creatinine in the high salt plus potassium citrate group ($P < 0.05$, potassium citrate *vs.* placebo, unpaired t test). Osteocalcin, PTH, and cAMP were not significantly altered. The addition of oral potassium citrate to a high-salt diet prevented the increased excretion of urine calcium and the bone resorption marker caused by a high salt intake. Increased intake of dietary sources of potassium alkaline salts, namely fruit and vegetables, may be beneficial for postmenopausal women at risk for osteoporosis, particularly those consuming a diet generous in sodium chloride. (*J Clin Endocrinol Metab* 87: 2008–2012, 2002)

OSTEOPOROSIS AND ITS sequelae pose a substantial health burden for postmenopausal women. One white woman in six will suffer a hip fracture during her lifetime, and mortality after hip fracture ranges from 12–20% in the first year. Modifications in nutrition can help reduce the risk of bone loss and fracture; for example, the benefit of adequate calcium and vitamin D intake is well documented (1, 2). Conversely, dietary sodium chloride has been considered potentially detrimental because increasing dietary sodium chloride increases urinary calcium excretion (3–9).

Renal calcium reabsorption is directly proportional to sodium reabsorption. When dietary sodium chloride is increased, the fractional reabsorption of sodium is decreased, leading to a parallel reduction in calcium reabsorption. Approximately 1 mmol calcium is excreted for every 100 mmol of sodium excreted (10). A net deficit of only 1 mmol/d of calcium would result in losing one third of the calcium contained in the typical adult skeleton in just over two decades unless a compensatory increase in intestinal calcium absorption occurred.

The ability to compensate for increased dietary sodium chloride may be related to age and menopausal status. In young men and premenopausal women, increased dietary sodium and consequent hypercalciuria induced an increase in calcitriol (1,25-dihydroxyvitamin D) levels and intestinal calcium absorption (11). However, postmenopausal women did not demonstrate increased calcitriol levels (12), suggesting that older women may be unable to compensate for urinary calcium losses induced by sodium.

Although the relationship between dietary sodium chloride and calcium excretion has been consistently demonstrated, studies have been mixed with regard to the effect of dietary salt on bone density and bone turnover markers, and potential interventions have not been examined. Therapies that decrease urinary calcium excretion could potentially prevent the calciuric effect of increased dietary sodium chloride. Alkaline salts of potassium (*e.g.* potassium bicarbonate, potassium citrate) significantly reduce urinary calcium excretion in young men and both premenopausal and postmenopausal women (13–15), even in the setting of a high sodium intake (16). Alkaline salts of potassium are a particularly attractive intervention as they occur naturally in fruits and vegetables. Amounts that decrease urinary calcium excretion could be consumed by increasing intake of fruits and vegetables.

In this study, we investigated the impact of increased dietary sodium chloride on urine calcium excretion, bone resorption, and bone formation in postmenopausal women and, further, whether oral potassium citrate attenuates the effects of increased dietary salt.

Subjects and Methods

Subjects

Sixty postmenopausal women were recruited through newspaper advertisements and direct mailings. Women were excluded if they were

Abbreviations: Cr, Creatinine; nMBCE, nanomoles bone collagen equivalent; NTX, N-telopeptide; UCSF, University of California San Francisco.

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less than 2 yr past menopause, on medications known to affect bone metabolism, or had evidence of metabolic bone disease by history, physical, or laboratory exam. Women were also excluded if they had conditions potentially worsened by increased dietary sodium such as congestive heart failure, uncontrolled hypertension, myocardial infarction within the previous 12 months, or cardiac arrhythmias. Additionally, women were excluded if they had contraindications to potassium supplementation, namely active gastrointestinal disease, renal insufficiency [2 h creatinine (Cr) clearance <40 ml/min, or serum Cr >2.0 mg/dl], metabolic acidosis (serum bicarbonate <16 mmol/liter), uncontrolled diabetes mellitus (fasting glucose >200 mg/dl), or medications altering potassium metabolism (angiotensin-converting enzyme inhibitors, β-blockers, potassium-sparing diuretics). To minimize differences in calcium intake, participants discontinued all personal calcium supplements 1–2 wk before starting the low-salt diet and were placed on calcium carbonate 500 mg/d throughout the study. This study was approved by the University of California San Francisco (UCSF) Institutional Review Board, and all participants provided informed consent.

Experimental protocol

After enrollment, a research dietitian instructed the study subjects in a diet containing 87 mmol/d (2000 mg) sodium. Participants were provided with information on reading food labels, lists of low-sodium foods, examples of low-sodium menus, and books listing the sodium content of common foods. Approximately 10 d into the low-salt diet, participants collected a 24-h urine sample to be assayed for sodium content to assess dietary compliance. Women whose urinary sodium was more than 10 mmol from the sodium intake goal were contacted, a 24-h dietary recall was performed to identify barriers to compliance, and the low-salt diet was reinforced. The subjects ingested the 87 mmol/d sodium diet for 3 wk. At the end of the third week, 24-h urine samples and fasting morning blood samples were collected in triplicate (three collections in the last 3–5 d of the low-salt diet). Triplicate collections were used to maximize precision, particularly in the 24-h urine collections because these samples were collected as outpatients.

After 3 wk on the low-salt diet, subjects began a high-sodium (225 mmol/d) diet: to the 87 mmol/d sodium diet, four oral sodium chloride pills, two weighed packets of salt to sprinkle on their food, and one cup of bouillon per day were added. Subjects were randomized to take either potassium citrate 90 mmol/d (UrocitK, Mission Pharmacal, San Antonio, TX) or indistinguishable placebo pills while on the high-salt diet. Approximately 12 d into the high-salt diet, participants collected a 24-h urine sample to assess dietary compliance. Again, women who were more than 10 mmol from the targeted sodium intake were contacted, barriers to compliance were rectified, and the high-salt regimen was reinforced. At the end of the fourth week on the high-salt diet, 24-h urine samples and fasting morning blood samples were collected in triplicate.

Randomization and blinding

Study drug was provided to the UCSF investigational pharmacy by the manufacturer in sealed bottles labeled "potassium citrate or placebo" and one of two lot numbers. Only the manufacturer knew the lot number that was potassium citrate and the lot number that was placebo. Participants were randomized using a random numbers list provided by the investigational pharmacy. All study personnel and the participants were blinded to the treatment groups throughout the study.

Biochemical assessment

Blood and urine samples were aliquoted and frozen at −70 C until all samples from a single participant were collected. All samples from each participant were analyzed in a single batch to prevent interassay differences. Sodium, potassium, and calcium were measured using standard techniques in the UCSF clinical laboratory.

Net acid excretion was calculated as the sum of the excretion rates of titratable acid and ammonium minus that of bicarbonate. Titratable acid concentration was determined by titration, and urine ammonium concentration was determined by the phenol method. Urine total carbon dioxide content was determined by thermal conductivity (CO_2 analyzer, CIBA Corning, Medfield, MA); the coefficient of variation of the method is 0.7%. Urine bicarbonate concentration was calculated from the measured values of urine pH and carbon dioxide content using the Henderson-Hasselbach equation, where the solubility coefficient of CO_2 is taken as 0.0309 and pK^I is corrected for ionic strength as follows: $pK^I = 6.33 - 0.5([Na^+] + [K^+])^{1/2}$, where Na^+ and K^+ concentrations are expressed in eq/liter.

Urinary N-telopeptides (NTX) of type I collagen and osteocalcin were measured using the ELISA method (Metra Biosystems, Palo Alto, CA). Intact PTH was measured using a two-site immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA). cAMP was measured using a RIA (INCSTAR Corp., Stillwater, MN).

Statistical analysis

The triplicate values from each participant at the end of each diet interval were averaged to provide a single low-salt and high-salt value for each participant. Within group analyses (comparing low salt to high salt in each group) were performed using a paired *t* test on the mean values at the end of the low- and high-salt periods. Between group analyses (comparing placebo and potassium citrate groups) were performed using an unpaired *t* test. For the between-groups analyses, outcomes were assessed as the difference in values between the low-salt and high-salt diets. All analyses were performed using STATA software (version 5.0, 1997; Stata Corp., College Station, TX).

Results

Baseline characteristics and subject withdrawals

Fifty-two (87%) of the women completed the 7-wk study; 26 had been randomized to placebo, and 26 had been randomized to potassium citrate. Eight women dropped out due to nausea from the sodium chloride pills on the high-salt diet. Women who withdrew from the study did not differ with respect to age, years since menopause, baseline sodium intake, compliance with the low-salt diet, or randomization to treatment or placebo. The characteristics at study entry (*i.e.* before the low-salt diet) of the women who completed the study are shown in Table 1.

Biochemical data

Urine sodium averaged 96 ± 5 mmol/d (mean ± SEM) on the low-salt diet and 235 ± 7 mmol/d on the high-salt diet. Compliance to the low- and high-salt diets, as evidenced by 24-h urine sodium excretion, was not different between the women randomized to potassium citrate and the women randomized to placebo.

TABLE 1. Characteristics of subjects at study entry (n = 52)

	High salt + placebo (n = 26)	High salt + potassium citrate (n = 26)
Age (yr)	63 ± 8	65 ± 8
Age at menopause (yr)	50 ± 4	50 ± 4
Urine sodium (mmol/d)	144 ± 51	138 ± 46
Serum calcium (mg/dl)	9.3 ± 0.1	9.4 ± 0.1
Urine calcium (mg/d)	215 ± 79	201 ± 101
Osteocalcin (ng/ml)	10.8 ± 3.2	10.7 ± 3.5
Urine NTX (nMBCE/mmol Cr)	47.0 ± 25.5	44.6 ± 28.6
Fasting PTH (pg/ml)	42.0 ± 13.0	45.6 ± 18.0
cAMP (nmol/liter)	2766 ± 779	2957 ± 829

Values are expressed as the mean ± SD. *P* value for comparison between women randomized to high salt plus placebo and women randomized to high salt plus potassium citrate by unpaired *t* test was not significant for all variables.

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Low-salt vs. high-salt plus placebo. In the women randomized to placebo, urine calcium excretion increased significantly from 200 ± 14 mg/d on the low-salt diet to 242 ± 16 mg/d on the high-salt diet plus placebo ($P = 0.002$). Urine NTX excretion increased significantly from 38.7 ± 4.2 nanomoles bone collagen equivalents (nMBCE)/mmol Cr on the low-salt diet to 45.1 ± 3.8 nMBCE/mmol Cr on the high-salt diet plus placebo ($P = 0.001$). Osteocalcin decreased slightly, but significantly, from 11.2 ± 0.6 ng/ml on the low-salt diet to 10.6 ± 0.6 ng/ml on the high-salt diet plus placebo ($P = 0.01$). There was no significant change in fasting PTH or cAMP between the low-salt and high-salt plus placebo diets. Additionally, urine potassium and net acid excretion were not different between the low-salt and high-salt diets in the women randomized to placebo (Table 2).

Low salt vs. high salt plus potassium citrate. In the women randomized to potassium citrate, urine calcium excretion decreased from 200 ± 14 mg/d on the low-salt diet to 192 ± 19 mg/d on the high-salt diet plus potassium citrate, a nonsignificant change ($P = 0.5$). Urine NTX excretion was 41.3 ± 3.6 nMBCE/mmol Cr on the low-salt diet and 43.3 ± 3.7 nMBCE/mmol Cr on the high-salt plus potassium citrate diet, a nonsignificant change ($P = 0.3$). There were no significant changes in osteocalcin, fasting PTH, or cAMP between the low-salt and high-salt plus potassium citrate diets. Urine potassium excretion increased from 70 ± 3 mmol/d on the low-salt diet to 141 ± 6 mmol/d on the high-salt diet plus potassium citrate ($P < 0.001$). Urine net acid excretion decreased from 32 ± 3 mmol/d on the low-salt diet to −28 ± 4 mmol/d on the high-salt plus potassium citrate diet ($P < 0.001$) (Table 2).

Potassium citrate vs. placebo. Urinary calcium excretion increased by 42 ± 12 mg/d (33%) between the low-salt and high-salt diet in the women randomized to high salt plus placebo, while decreasing by 8 ± 14 mg/d (4%) in the women randomized to high salt plus potassium citrate. The difference between the two groups was significant ($P = 0.008$). Urinary NTX excretion increased by 6.4 ± 1.4 nMBCE/mmol Cr (23%) between the low-salt and high-salt diets in the women randomized to high salt plus placebo, while increasing by 2.0 ± 1.7 nMBCE/mmol (7.5%) in the women randomized to high salt plus potassium citrate. The change in urine NTX excretion was significantly different between the two groups ($P < 0.05$) (Table 3). There was no significant difference between the two groups in changes in osteocalcin, fasting PTH, or cAMP. Between the low- and high-salt diets, urine potassium increased by 2 ± 3 mmol/d in the women randomized to high salt plus placebo, while increasing by 72 ± 5 mmol/d in the women randomized to high salt plus potassium citrate, a significant difference ($P < 0.001$). Urine net acid excretion decreased by 3 ± 3 mmol/d between the low-salt and high-salt diets in the women randomized to high salt plus placebo, while decreasing by 60 ± 5 mmol/d in the women randomized to high salt plus potassium citrate; the difference between the two groups was significant ($P < 0.001$).

TABLE 2. Calcium, bone markers, and hormones: low salt (87 mmol/d sodium) *vs.* high salt (225 mmol/d sodium) plus placebo and low salt *vs.* high salt plus potassium citrate (90 mmol/d)

	Women randomized to placebo (n = 26)			Women randomized to potassium citrate (n = 26)		
	Low salt	High salt	*P* value *vs.* low salt	Low salt	High salt	*P* value *vs.* low salt
Urine calcium (mg/d)	200 ± 14	242 ± 16	0.002	200 ± 14	192 ± 19	0.5
Urine NTX (nMBCE/mmol Cr)	38.7 ± 4.2	45.1 ± 3.8	0.001	41.3 ± 3.6	43.3 ± 3.7	0.3
Serum calcium (mg/dl)	9.4 ± 0.1	9.4 ± 0.1	0.5	9.4 ± 0.1	9.4 ± 0.1	0.4
Osteocalcin (ng/ml)	11.2 ± 0.6	10.6 ± 0.6	0.01	10.9 ± 0.7	10.7 ± 0.6	0.3
Fasting PTH (pg/ml)	41.7 ± 2.7	42.7 ± 2.9	0.5	49.2 ± 3.8	48.5 ± 3.4	0.7
cAMP (nmol/liter)	2630 ± 132	2783 ± 144	0.2	3013 ± 185	3043 ± 157	0.8
Urine potassium (meq/d)	75 ± 4	77 ± 4	0.6	70 ± 3	141 ± 6	<0.001
Net acid excretion (meq/d)	28 ± 4	25 ± 3	0.3	32 ± 3	−28 ± 4	<0.001

All values are mean ± SEM. The *P* value is for comparison between the low-salt and high-salt diets by paired *t* test within each group (placebo or potassium citrate).

TABLE 3. Change in calcium, bone turnover markers, and hormones from low salt (87 mmol/d sodium) to high salt (225 mmol/d sodium), placebo *vs.* potassium citrate (90 mmol/d)

	Change from low salt to high salt + placebo	Change from low salt to high salt + potassium citrate	*P* value placebo *vs.* potassium citrate
Urine calcium (mg/d)	42 ± 12	−8 ± 14	0.008
Urine NTX (nMBCE/mmol Cr)	6.4 ± 1.4	2.0 ± 1.7	0.049
Serum calcium (mg/dl)	0.04 ± 0.06	0.05 ± 0.05	0.89
Osteocalcin (ng/ml)	−0.57 ± 0.21	−0.22 ± 0.23	0.26
Fasting PTH (pg/ml)	0.97 ± 1.5	−0.74 ± 1.8	0.46
cAMP (nmol/liter)	142.2 ± 99.2	106.7 ± 135.6	0.83
Urine potassium (meq/d)	2 ± 3	72 ± 5	<0.001
Net acid excretion (meq/d)	3 ± 3	60 ± 5	<0.001

Values are expressed as the mean ± SE. The *P* value is for comparison between women randomized to high salt plus placebo and women randomized to high salt plus potassium citrate by unpaired *t* test.

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Discussion

Although the effects of dietary sodium chloride on urine calcium excretion have been consistent, the effect on bone density, bone loss, and bone turnover is less clear. Dietary sodium has not been associated with bone mineral density in two cohorts in the United States (17, 18), and studies of the relationship between dietary sodium and bone loss have been mixed (19, 20). Cross-sectional studies have demonstrated a positive correlation between sodium and calcium excretion and urinary hydroxyproline (5, 6, 21), and hydroxyproline excretion appears to increase with salt administration (4, 22). However, of the two intervention studies using a more specific marker of bone resorption, deoxypyridinoline, one demonstrated an increase in bone resorption with increased dietary salt (23), but the other did not (24).

We found that increased dietary salt increased urinary calcium excretion in the women randomized to the high-salt diet plus placebo. Enhanced calcium excretion was associated with increases in a marker of bone resorption, NTX, suggesting that the increased calcium excretion due to increased dietary salt has skeletal effects. Additionally, the marker of bone formation, osteocalcin, was slightly, but significantly, reduced. The increased urinary calcium loss in the high salt plus placebo group did not result in changes in fasting PTH or cAMP, suggesting that, as seen in previous studies (12), postmenopausal women eating abundant salt do not show hormonal responses that could compensate for enhanced urinary calcium losses.

In contrast, urinary calcium and NTX excretion in the women randomized to high salt plus potassium citrate during the high-salt diet were not different from on the low-salt diet, despite increased urine sodium excretion. Additionally, the women taking potassium citrate during the high-salt diet were significantly different from the high salt plus placebo group with regard to changes in urine calcium and NTX, suggesting that potassium citrate prevented the increased calcium and bone resorption biomarker excretion caused by increased salt intake.

The ability of potassium citrate to reduce urine calcium excretion and markers of bone turnover may be multifactorial. Alkaline salts of potassium are both natriuretic and chloruretic, potentially reducing the extracellular volume expansion that occurs with increased salt intake. This effect may be partly responsible for the decreased calcium excretion that occurs when these agents are given with a high-salt diet (16). In our study, the addition of potassium citrate and sodium chloride to a low-salt diet resulted in no difference in urine calcium excretion compared with a low-salt diet.

In addition to effects on extracellular volume, alkaline salts of potassium reduce endogenous acid production and increase blood pH and plasma bicarbonate concentration (25, 26). Urinary calcium excretion varies directly with endogenous acid production as measured by urinary net acid excretion; increased net acid excretion is associated with decreased renal tubular reabsorption of calcium (27). In our study, net acid excretion decreased by 60 mmol/d in the women given potassium citrate; in fact, the average net acid excretion in this group was negative. This appears to be a significant factor; in our study, urine calcium and bone turnover markers were no different on a high-salt diet with potassium citrate than on a low-salt (87 mmol/d sodium) diet alone. Additionally, potassium itself may be a factor in calcium excretion. Potassium deficient diets are associated with increased urine calcium excretion, potassium supplementation reduces urinary calcium excretion (14, 25, 28), and potassium appears to have a direct effect on the kidney to promote calcium reclamation (29). Finally, the total sodium and chloride content of the diet may also be important. Sodium bicarbonate can improve calcium balance when substituted for sodium chloride in the diet (30). However, when dietary sodium chloride remains constant or is increased, potassium bicarbonate, but not sodium bicarbonate, improves calcium balance (13).

Our study examined the effects of dietary sodium chloride and oral potassium citrate over 1 month. Previous studies examining the effect of high-salt diets on bone turnover markers have been limited to 7–10 d. This study suggests that the effect of increased dietary sodium chloride could be ongoing. Larger studies with more long-term outcomes such as bone mineral density and fracture will be needed to define the role of dietary sodium chloride in postmenopausal bone loss and osteoporosis more completely.

However, the results of this randomized, double blind, placebo-controlled trial suggest that increased dietary salt not only enhances urinary calcium excretion, but also results in increased excretion of bone resorption biomarkers. The addition of oral potassium citrate to a high-salt diet prevented the increased calcium losses and rise in bone turnover markers caused by a high dietary salt intake. Prior investigations have also suggested that higher intake of dietary potassium and potassium-rich foods, namely fruit and vegetables, is associated with higher bone density in both pre- and postmenopausal women (31, 32). The amount of potassium that reduced urine calcium excretion and NTX in our study could be ingested by consuming 7–8 servings of potassium-rich fruit and vegetables each day.

Current dietary guidelines recommend moderate sodium intake (2400 mg/d), but research on the impact of dietary sodium has focused primarily on the cardiovascular system. This study provides further evidence that recommendations regarding moderate sodium intake and increased intake of dietary sources of potassium alkaline salts, namely fruit and vegetables, may also be beneficial to postmenopausal women at risk for osteoporosis.

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