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Long-term combined treatment with thiazide and potassium citrate in nephrolithiasis does not lead to hypokalemia or hypochloremic metabolic alkalosis

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Long-term combined treatment with thiazide and potassium citrate in nephrolithiasis does not lead to hypokalemia or hypochloremic metabolic alkalosis.

Background. Potassium citrate is commonly used in combination with a thiazide diuretic in the medical management of recurrent hypercalciuric nephrolithiasis. However, concerns have been raised that administration of this nonchloride potassium alkali with a kaliuretic and natriuretic agent such as thiazide may not be efficacious in correcting or preventing hypokalemia, and may produce hypochloremic metabolic alkalosis. This retrospective analysis was conducted to determine if these two potential complications are encountered in patients on long-term potassium citrate and thiazide therapy.

Methods. Data were collected on 95 patients who had been on combination therapy for at least 4 months from the stone clinics of the University of Texas Southwestern Medical Center, Duke University Medical Center, and Ochsner Clinic.

Results. Mean serum potassium concentration remained within normal limits without a significant decrease during combined therapy. Serum chloride was significantly lower from pretreatment but by only 1 mEq/L and remained within normal limits throughout treatment. There was a small increase in serum bicarbonate concentration compared to the baseline level of less than 1 mEq/L at 8 to 12 and 18 to 24 months, but not at other treatment periods.

Conclusion. Co-administration of potassium citrate did not induce hypokalemia or hypochloremic metabolic alkalosis in our thiazide-treated patient population.

Thiazide diuretics are commonly used for the prevention of recurrent calcium oxalate nephrolithiasis [1, 2] owing to their hypocalciuric action [3]. Inherent in the therapeutic effects of thiazide diuretics is urinary potassium wasting. Even mild degrees of potassium depletion can lead to intracellular acidosis and hypocitraturia [4, 5] that offset the therapeutic advantage of lowering urinary calcium. Therefore, thiazide therapy invariably obligates some form of potassium replacement. Potassium citrate in combination with a thiazide diuretic has been shown to be useful in the medical management of recurrent hypercalciuric nephrolithiasis [6]. In addition to the replenishing of potassium, potassium citrate has the added advantage of increasing urinary pH and urinary citrate, rendering it a suitable agent in the medical management of patients with hypercalciuric nephrolithiasis taking thiazide.

Two concerns have been raised about using an alkali organic anion such as citrate rather than chloride as part of the potassium supplement for patients on long-term thiazide therapy. First, potassium from potassium chloride is much better retained than from potassium citrate or bicarbonate, rendering patients on potassium citrate more prone to develop chronic potassium depletion [7]. Second, an alkali given in conjunction with a natriuretic may increase the risk for the development of metabolic alkalosis [8]. Theoretically, these complications, if present, may negate the advantages of potassium citrate stated above.

This retrospective analysis was undertaken to specifically determine if administration of potassium citrate is effective in preventing thiazide-induced hypokalemia and whether there is any evidence of metabolic alkalosis. Data on 95 patients were analyzed from medical records from three centers specializing in the care of patients with nephrolithiasis. The present study indicates that hypokalemia does not develop during long-term thiazide therapy, and that hypochloremic alkalosis is not a major problem when potassium citrate is a component of the treatment regimen.

Key words: thiazide, potassium citrate, metabolic alkalosis, nephrolithiasis.

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METHODS

Study population

All patients were selected from three stone clinics at the University of Texas Southwestern Medical Center, Dallas, Texas (group 1), Duke University Medical Center, Durham, North Carolina (group 2), and the Ochsner Clinic, New Orleans, Lousiana (group 3) and satisfied five criteria: (*1*) idiopathic calcium oxalate nephrolithiasis, defined as calcium oxalate stone formation, without evidence of chronic diarrheal syndrome, primary hyperparathyroidism, complete distal renal tubular acidosis, cystinuria, or infection stones; (*2*) persistent or intermittent hypercalciuria that was thought sufficient to qualify for thiazide treatment; (*3*) absence of hypokalemia, hyperkalemia or predisposition to hyperkalemia (such as type IV renal tubular acidosis or treatment with angiotensin-converting enzyme inhibitors or large doses of nonsteroidal anti-inflammatory agents); (*4*) normal renal function (creatinine clearance, obtained from fasting serum and 24-hour urinary creatinine at initial evaluation, of greater than 0.7 mL/min/kg); and (*5*) concurrent administration of thiazide and potassium citrate (begun together) for at least 1 year from group 1, and at least 4 months from groups 2 and 3. Patients from group 1 were generally followed every 4 months during treatment, whereas those from groups 2 and 3 were typically followed every 6 months. No one with side effects to treatment was excluded.

Laboratory analysis

For patients from all three groups, fasting venous blood samples for measurement of sodium, potassium, chloride, and bicarbonate were drawn before treatment and at each follow-up treatment visit. At each institution, the above tests were obtained from Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories. From group 1 only, 24-hour hour urine samples were collected for the measurement of complete urinary stone risk factors, which included potassium, pH, citrate, sodium and chloride, using methods previously described [9]. From the urinary biochemical data, net gastrointestinal absorption of alkali [10] and titratable acidity were calculated [11]. All 24-hour urine samples were collected with the patients on ad libitum outpatient diets.

Drug and dose selection

The physicians caring for the patients chose the type and dose of thiazide, based on their experience in managing hypercalciuria. Physicians also selected the dose of potassium citrate from their perception of the amount required to prevent hypokalemia and hypocitraturia.

Generic preparations of hydrochlorothiazide were generally used. Some patients initially received the brand form of trichlormethiazide (Naqua, Schering Corp., Kenilworth, NJ, USA) but were later switched to the generic preparations when they became available. A tablet formulation of potassium citrate (Urocit-K, 10 mEq tablets in wax matrix, Mission Pharmacal Co., San Antonio, TX, USA) was used. Six patients who took hydrochlorothiazide took amiloride as well (Moduretic, Merck & Co., Inc., West Point, PA, USA).

Table 1. Study population and treatment

	Group 1 $N = 50$	Group 2 $N = 23$	Group 3 $N = 22$
Patients			
Males	41	18	12
Females	9	5	10
Age *years*, mean (range)	48 (15–75)	47 (27–66)	55 (32–77)
Treatment dose *mean ± SD*			
Trichlormethiazide *mg/day*	3 ± 1	3 ± 1	
Hydrochlorothiazide *mg/day*	53 ± 18	50	34 ± 25
Urocit-K *mEq/day*	40 ± 16	40 ± 8	52 ± 19
Duration of treatment *months*, mean (range)	27 (12–36)	19 (4–50)	35 (12–81)

Statistical analysis

Repeated analysis of variance was used to test for significant changes between pretreatment and treatment periods. Significant difference between two values before and after treatment was assessed by paired *t* test. Since there was no study site interaction, results from the three groups were combined. A combination of thiazide (50 mg) and amiloride (5 mg) typically produces a milder degree of hypokalemia without potassium supplementation. Exclusion of six patients on this combination did not alter the results. Thus, data in all patients were presented.

RESULTS

Study population and treatment

Ninety-five patients were analyzed in this retrospective analysis comprising 50 patients from group 1, 23 from group 2, and 22 from group 3 (Table 1). The cause of hypercalciuria was rigorously sought with "fast and calcium load test" [12] and serum parathyroid hormone (PTH) only in group 1. Forty-four of 50 patients from group 1 had absorptive hypercalciuria. The remaining six patients had persistent or intermittent hypercalciuria of undetermined origin, along with gouty diathesis in three and hypercalciuric calcium oxalate nephrolithiasis in three. In groups 2 and 3, the cause of hypercalciuria was not established as precisely. The majority of patients were men (Table 1). Mean dose and duration of treatment are summarized in Table 1. In group 1, 31 patients were on trichlormethiazide at an average dose of 3.0 mg/day, and 19 were taking hydrochlorothiazide 53 mg/day, six of them with amiloride 5 mg/day. In group 2, 22 patients were on trichlormethiazide at an average dose

Table 2. PTH, serum calcium and serum electrolytes before and during combined treatment with Urocit-K and thiazide

	Treatment duration *months*				
	Baseline	4–6	8–12	18–24	>24
Sodium *mEq/L*	140 ± 3	140 ± 3	140 ± 2	140 ± 2	140 ± 2
Potassium *mEq/L*	4.15 ± 0.36	4.20 ± 0.39	4.19 ± 0.37	4.20 ± 0.38	4.12 ± 0.35
Chloride *mEq/L*	103 ± 3	102 ± 3[b]	102 ± 3[c]	102 ± 3[c]	102 ± 3[b]
Bicarbonate *mEq/L*	26.2 ± 2.5	26.5 ± 2.7	26.9 ± 2.7[a]	27.1 ± 2.6[c]	26.9 ± 2.6
Calcium *mg/dL*	9.5 ± 0.3				
Parathyroid hormone					
Mid molecule[d] *pg/mL*	275 ± 126				
Intact[e] *pg/mL*	36 ± 17				

Data presented as mean ± SD. Statistical significance from baseline indicated by
[a] $P < 0.05$; [b] $P < 0.01$, and [c] $P < 0.005$
[d] Normal value 100–400 pg/mL
[e] Normal value: 10–65 pg/mL

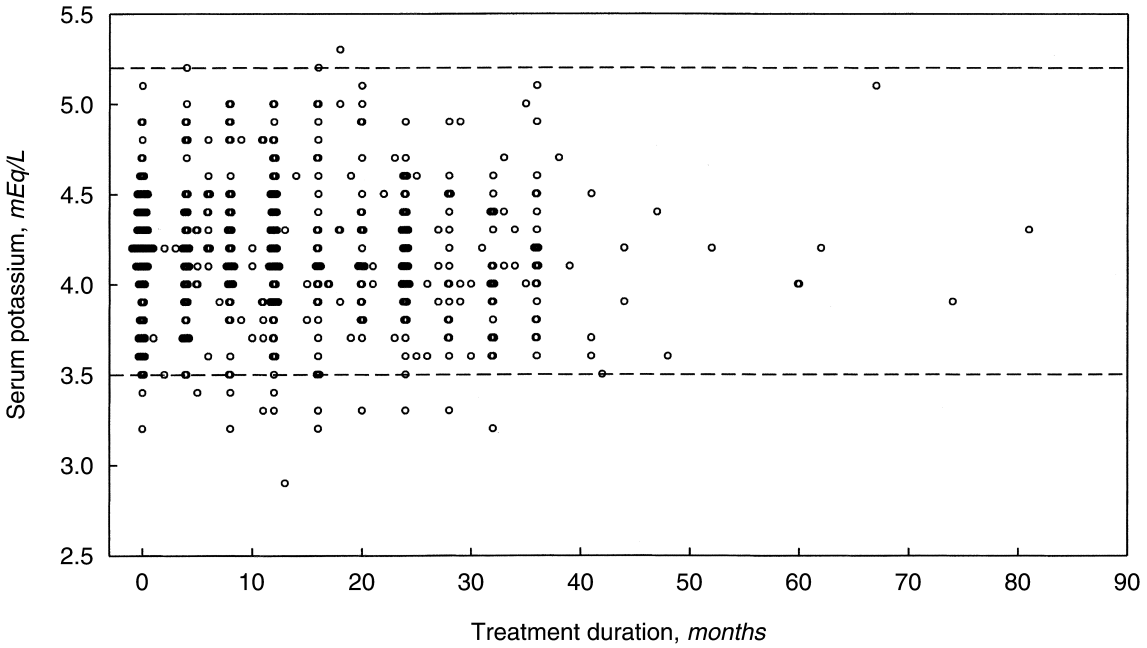

Fig. 1. Individual serum potassium values during combined treatment with thiazide and potassium citrate. Majority of the values were within normal limits. Thirteen determinations (from six patients) were less than 3.5 mEq/L. The patient who had persistent hypokalemia from months 8 to 32 was taking a large dose of hydrochlorothiazide (100 mg/day) and had both absorptive hypercalciuria and incomplete renal tubular acidosis. Dashed horizontal lines indicate the normal range. Individual points are depicted. Some points appear darker than others because of close similarity in values among several samples.

of 3 mg/day, and one was on hydrochlorothiazide 50 mg/day. In group 3, all 22 patients were on hydrochlorothiazide at an average dose of 34 mg/day. Mean dose of potassium citrate was 40 mEq/day for groups 1 and 2. Despite a lower dose of thiazide, the dose of potassium citrate was slightly higher at 52 mEq/day in group 3. The duration of thiazide-potassium citrate treatment ranged from 4 to 81 months; mean duration ranged from 19 to 35 months at the three sites.

Serum chemistries

Serum data from the three centers were pooled and analyzed. Mean serum potassium was normal at baseline and remained within normal limits throughout the combined treatment with potassium citrate and thiazide (Table 2). Serum calcium and PTH measured in 45 patients at baseline were within normal limits. Individual potassium values are presented in Figure 1. At baseline, two patients had hypokalemia (<3.5 mEq/L), and no one had a potassium concentration >5.2 mEq/L. Of 414 determinations from 95 patients during repeat follow-up visits, serum potassium concentration was below 3.5 mEq/L in 13 determinations (from six patients). In five of these patients, hypokalemia was corrected with increased dose of potassium citrate. Only one patient had persistently low potassium concentration (in months 8

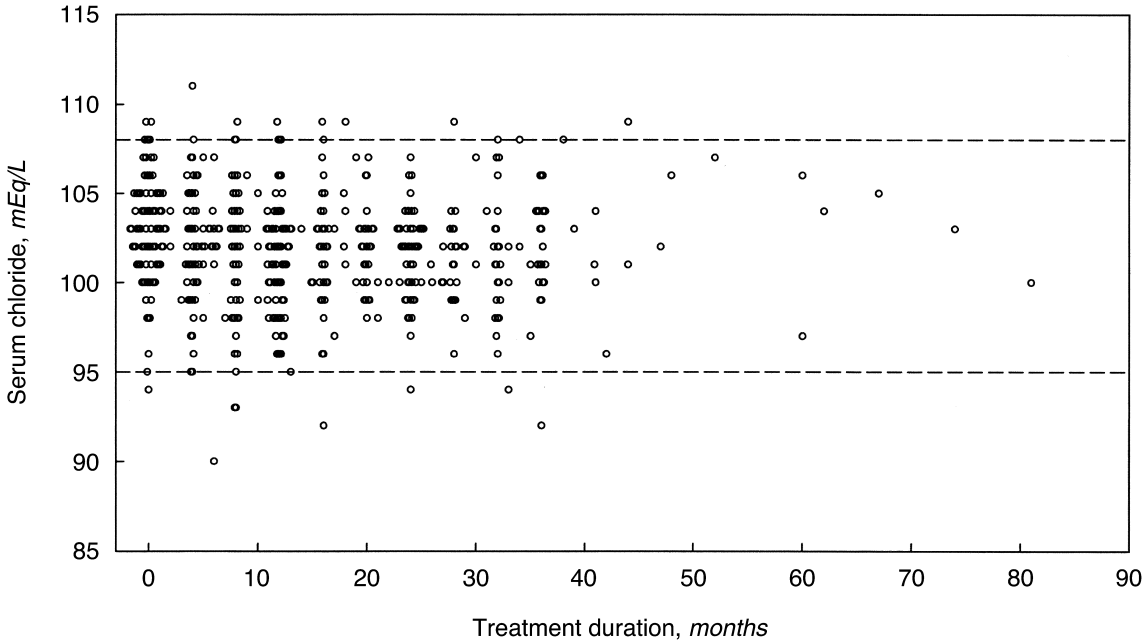

Fig. 2. Individual serum chloride values during combined treatment with thiazide and potassium citrate. During combined therapy, the majority of the patients remained normochloremic. Only five patients developed transient decrease in serum chloride concentration, and six had serum chloride concentrations >108 mEq/L. Dashed horizontal lines indicate the normal range.

to 32). This patient had absorptive hypercalciuria and incomplete distal renal tubular acidosis and was taking 100 mg hydrochlorothiazide/day. Eventually, hypokalemia was corrected when the dose of potassium citrate was increased to 100 mEq per day. Among 414 determinations during follow-up visits, only one potassium determination (from one patient) was greater than 5.2 mEq/L.

Mean serum chloride was slightly and significantly lower by 1 mEq/L from baseline, but remained within normal limits during combined thiazide-potassium citrate therapy (Table 2). Individual values are plotted over varying periods of treatment in Figure 2. Before treatment, one patient had hypochloremia (serum chloride <95 mEq/L) and two patients had high serum chloride concentration (>108 mEq/L). Among 413 samples during combined treatment with thiazide and potassium citrate, seven determinations (from five patients) were low and seven determinations from six patients were above 108 mEq/L.

Mean serum bicarbonate (total carbon dioxide) concentration was slightly and significantly higher compared to pretreatment value at 8 to 12 months and 18 to 24 months of combined thiazide-potassium treatment, but was not significantly different from baseline at other treatment periods (Table 2). All mean serum bicarbonate concentrations remained within normal limits during the entire period of combined treatment. Individual values are shown in Figure 3. At baseline, one determination from one patient was low (<20 mEq/L). None of the patients had high (>32 mEq/L) bicarbonate concentration. Among 401 determinations from all 95 patients during combined treatment, three determinations from two patients were low, and six determinations from four patients were >32 mEq/L.

Results were indistinguishable when six patients who took amiloride were excluded compared with data from all patients. Similar trends were observed among the threee groups even though patients in group 3 received relatively lower dose of thiazide and higher dose of potassium citrate (Table 1). There was no significant change in serum sodium concentration during combined treatment compared to baseline (Table 2).

Urinary chemistries

Pertinent urinary chemistries, available from group 1 only, are presented in Table 3. Compared with pretreatment, combined treatment with thiazide and potassium citrate produced a significant and sustained rise in urinary pH, citrate, and potassium. Urinary potassium increased by an average of 40 mEq, approximating the amount of potassium given as replacement. Urinary pH increased by an average of 0.55 and was maintained between 6.3 and 6.5. The mean increase in urinary citrate was 209 ± 45 mg during combined therapy. Urinary sodium and chloride did not significantly change during combined therapy.

Urinary chloride was measured in most ($N = 38$) but not all patients or visits from group 1. Thus, the net gastrointestinal alkali absorption and titratable acidity could not be calculated in some patients or visits. Urinary

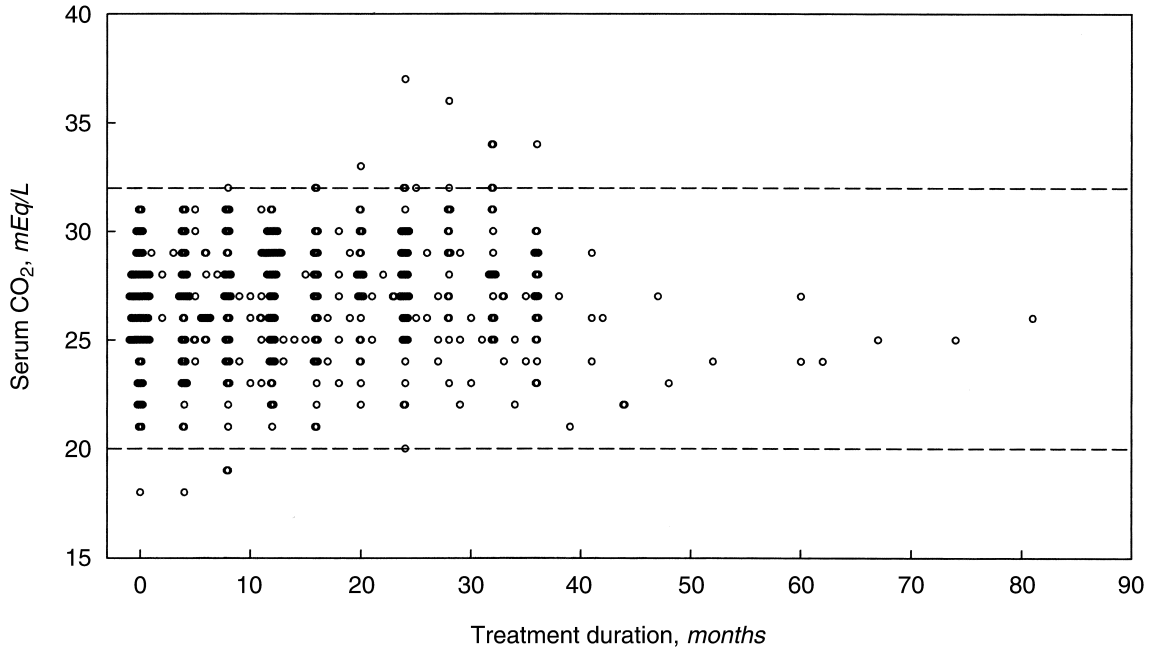

Fig. 3. Individual serum bicarbonate [total carbon dioxide (CO_2)] concentrations during combined treatment with thiazide and potassium citrate. Most of the values were within normal limits during combined therapy. Only three out of 401 determinations were <20 mEq/L and six determinations from four patients were >32 mEq/L. The dashed horizontal lines indicate the normal range.

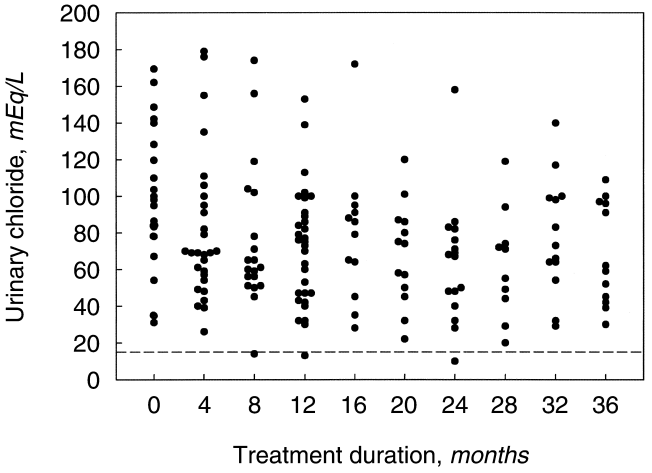

Fig. 4. Individual urinary chloride concentrations before and during treatment. Urinary chloride concentration was rarely (three out of 154 determinations) below 15 mEq/L during combined therapy.

chloride concentration was rarely below 15 mEq/L (3 of 154 determinations from three patients during combined thiazide-potassium citrate treatment). Compared with pretreatment, net gastrointestinal alkali absorption significantly increased while titrable acidity decreased significantly during combined treatment (Table 3).

DISCUSSION

This study was prompted by a long-held concern that nonchloride potassium salt such as potassium citrate given with thiazide may be ineffective in averting hypokalemia and may produce hypochloremic metabolic alkalosis [8]. This retrospective analysis from 95 patients with calcium oxalate stones at three established stone clinics indicate that neither complication occurs during long-term combined treatment with thiazide and potassium citrate. Thiazide reduces urinary calcium excretion by its indirect effect from extracellular volume contraction and its primary stimulation of distal renal tubular reabsorption of calcium through unresolved mechanisms [13, 14]. This "hypocalciuric" action renders thiazide an effective agent in the management of hypercalciuric calcium oxalate nephrolithiasis. A review by Coe of randomized trials indicated inhibition of stone recurrence by thiazide [15].

Recent studies disparaging the role of dietary calcium restriction in stone formation should not detract from the ability of thiazide to inhibit stone formation. Borghi et al found a low protein-sodium diet to be more effective than low calcium diet in inhibiting stone formation [16]. Several epidemiological studies by Curhan et al [17, 18] among subjects without stones indicated that high calcium diet may be protective against stone formation. These studies indicating negative effect of dietary calcium restriction were attributed to the concurrent increase in urinary oxalate. However, no one disputes the fact that hypercalciuria increases the risk for calcium oxalate stone formation [19, 20]. Curhan et al reported that hypercalciuria carried a high risk for stone formation among patients with stones [21]. The advantage of thia-

Table 3. Effect of combined thiazide-potassium treatment on urinary parameters

	Treatment duration *months*								
	Baseline	4	8	12	16	20	24	28	32	36
Total volume *L/day*	1.99 ± 0.91	2.56 ± 0.99[c]	2.50 ± 0.97[c]	2.54 ± 0.94[c]	2.52 ± 0.79[c]	2.89 ± 0.77[c]	2.75 ± 0.80[c]	2.86 ± 0.71[c]	2.77 ± 0.82[c]	2.73 ± 0.60[c]
pH	5.96 ± 0.42	6.44 ± 0.43[c]	6.35 ± 0.50[c]	6.44 ± 0.49[c]	6.44 ± 0.49[c]	6.47 ± 0.42[c]	6.51 ± 0.50[c]	6.34 ± 0.52[c]	6.49 ± 0.39[c]	6.63 ± 0.41[c]
Citrate *mg/day*	500 ± 244	680 ± 277[c]	709 ± 417[c]	707 ± 338[c]	721 ± 428[c]	554 ± 254[b]	772 ± 399[c]	591 ± 284[c]	752 ± 312[c]	714 ± 282[c]
Potassium *mEq/day*	53 ± 16	86 ± 27[c]	90 ± 38[c]	86 ± 33[c]	88 ± 34[c]	89 ± 33[c]	90 ± 38[c]	88 ± 33[c]	90 ± 32[c]	94 ± 38[c]
Sodium *mEq/day*	180 ± 72	194 ± 80	175 ± 85	186 ± 81	208 ± 105	181 ± 69	196 ± 78	194 ± 59	194 ± 67	204 ± 66
Chloride *mEq/day*	168 ± 83	185 ± 75	156 ± 77	169 ± 65	173 ± 78	197 ± 68	149 ± 55	160 ± 59	194 ± 61	167 ± 52
NGIA *mEq/day*	39 ± 38	65 ± 33[a]	73 ± 75[b]	73 ± 51[c]	71 ± 36[a]	54 ± 35	82 ± 47[c]	70 ± 63[a]	57 ± 27	100 ± 73[c]
Titratable acidity *mEq/day*	22.5 ± 8.7	15.7 ± 10.0[c]	16.0 ± 10.7[c]	16.5 ± 12.6[c]	15.9 ± 12.4[c]	14.6 ± 8.5[c]	15.0 ± 11.2[c]	17.4 ± 10.0[a]	14.4 ± 7.5[c]	11.2 ± 8.0[c]

NGIA is net gastrointestinal absorption of alkali.
Data presented as mean ± SD. Statistical significance from baseline indicated by [a] $P < 0.05$, [b] $P < 0.01$, and [c] $P < 0.005$.

zide is that it can reduce urinary calcium without affecting urinary oxalate [22].

Despite the utility of thiazide in the management of hypercalciuric calcium oxalate nephrolithiasis, its kaliuretic effect mandates concomitant potassium replacement with its use. Because of the urinary alkalinizing and citraturic effects [23], citrate is the preferred anion for administering potassium when treating hypercalciuric patients with thiazide. Previous placebo-controlled randomized trials have shown that potassium alkali can decrease stone recurrence rate in patients with idiopathic hypocitraturic calcium nephrolithiasis [24, 25].

However, two potential complications of combined treatment with thiazide and potassium citrate have been raised. First, while the administration of alkali to normal subjects results in bicarbonaturia with no rise in serum bicarbonate, the same dose of alkali when given to individuals with diuretic-induced volume contraction might result in alkali retention and metabolic alkalosis [26]. Although this may be a potential complication of combination thiazide-potassium citrate therapy for patients with hypercalciuria, available data failed to show metabolic alkalosis during combined therapy [27, 28]. Retention of exogenously administered alkali occurs under nonphysiologic maneuvers involving gastric suction and/or very low sodium diets [29, 30]. In this study of patients with nephrolithiasis, we used a less potent thiazide. Moreover, severe sodium restriction is practically impossible to achieve in the outpatient setting over months among patients with stones.

Second, Atkins and Schwartz, in experimental animals [31], and Kassirer et al, in human subjects [8], have noted that it is not possible to correct hypokalemic hypochloremic alkalosis with potassium administration unless chloride is provided. These investigators proposed that the reduced delivery of chloride from a nonchloride potassium salt would impair the renal tubular reabsorption of sodium as sodium chloride, favoring hydrogen and potassium excretion, which would perpetuate or accelerate the metabolic alkalosis and persistent hypokalemia.

A later study by Carlisle et al showed that the poorly reabsorbable anions such as sulfate or bicarbonate increase renal potassium secretion [32]. When the urinary concentration of chloride was greater than 15 mEq/L, sulfate does not increase renal potassium excretion but bicarbonate can still be kaliuretic. In this study, and generally in stone patients on normal diets, urinary chloride is greater than this value in the vast majority of patients (Fig. 4). Urinary chloride concentration less than 15 mEq/L would be expected to occur only among patients with intractable or severe vomiting, diarrhea, or sweating.

Nonetheless, since these concerns have been raised, we conducted this retrospective analysis of data from three centers to determine if the use of potassium citrate with

a thiazide diuretic is effective in preventing hypokalemia, and whether metabolic alkalosis is encountered.

In patients who have been on treatment for at least 4 to 81 months (a mean of 19 to 35 months at three centers), serum potassium concentration remained within normal limits in majority (>90%) of the patients during potassium citrate supplementation. This finding supports our contention that potassium citrate prevents diuretic-induced hypokalemia. This finding had been reported before in a randomized short-term treatment trial [28, 33], as well as in a long-term trial [27]. We have shown in previous studies that hypokalemia would have developed if thiazide is administered without potassium citrate supplementation [34].

Consistent with previously published reports, administration of potassium citrate provided an alkali load, since it resulted in significant and sustained increase in urinary pH, citrate, net gastrointestinal absorption of alkali and titratable acidity [35]. The resulting rise in urinary citrate conferred protection against calcium stone formation [36]. Although there was a statistically significant difference in serum chloride and bicarbonate toward hypochloremic metabolic alkalosis, these changes occurred within normal limits and were not clinically significant in magnitude. These effects, in fact, may be advantageous in the management of patients with hypercalciuric nephrolithiasis many of whom present with evidence of bone loss [37]. Potassium alkali may prevent bone loss in postmenopausal osteoporosis [38], as well as in recurrent calcium oxalate nephrolithiasis [39].

The present study has a number of limitations. First, there is no control group. Typically, a group taking hydrochlorothiazide and placebo would serve as a control to establish the incidence of hypokalemia and metabolic alkalosis without potassium citrate. However, it would be unethical to withhold potassium replacement from patients who are on chronic thiazide therapy. Previous studies have shown that hypokalemia develops within 3 weeks of thiazide therapy [40] and persists, after it develops during chronic therapy, if potassium replacement is not initiated [41]. On the other hand, one might argue that an appropriate control group would be patients treated with thiazide and potassium chloride. This has been addressed by an earlier study by Nicar, Peterson, and Pak [33], which showed that potassium citrate is equally effective as potassium chloride in controlling hypokalemia in the setting of adequate chloride intake. In addition, serum bicarbonate and chloride concentrations were not significantly different in the two treatment groups. Moreover, the present analysis was not aimed at comparing different potassium replacement regimens but rather to demonstrate the lack of hypokalemia and metabolic alkalosis in combined thiazide/potassium citrate therapy. Finally, this is a retrospective study and the doses of thiazide and potassium citrate were not uniform. One has to acknowledge that this is not unusual in clinical practice because of variable individual response to treatment. If there is a dose effect, we should have seen a between-group difference in serum electrolyte changes on combined therapy. This was not evident when the data from the three groups were analyzed separately (data not shown).

In summary, the present study provides evidence that administration of potassium citrate can effectively maintain normokalemia and does not lead to metabolic alkalosis during long-term thiazide therapy for hypercalciuric nephrolithiasis.

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