

## DIETARY MANIPULATION WITH LEMONADE TO TREAT HYPOCITRATURIC CALCIUM NEPHROLITHIASIS

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### ABSTRACT

**Purpose:** Pharmacological treatment of hypocitraturic calcium nephrolithiasis requires as many as 12 tablets, or numerous crystal packages or liquid supplements taken throughout the day. In addition to added cost, this cumbersome regimen decreases patient compliance, which may increase stone recurrence rates. We evaluated the urinary biochemical effects of dietary citrate supplementation in hypocitraturic calcium stone formers in an attempt to decrease or eliminate the need for pharmacological therapy.

**Materials and Methods:** A total of 12 patients who were either noncompliant with or intolerant of pharmacological citrate therapy supplemented their routine diet with citrate in the form of lemonade, consisting of 4 ounces of reconstituted lemon juice (5.9 gm. citric acid) mixed with tap water to a total volume of 2 l. and consumed at uniform intervals throughout the day. Urine specimens (24-hour) were obtained for biochemical analysis after 6 days of lemonade therapy and compared to pre-lemonade baseline values.

**Results:** Of the 12 patients 11 had increased urinary citrate levels during lemonade therapy (average 204 mg. per day). Average levels increased from 142 mg. daily (range less than 10 to 293) at baseline to 346 mg. daily (range 89 to 814) after treatment ( $p < 0.001$ ). Daily total urinary volumes were similar (2.7 versus 2.9 l.). Seven of 12 patients became normocitraturic while consuming lemonade. Urinary calcium excretion decreased an average of 39 mg. daily, while oxalate excretion was unchanged. The lemonade mixture was well tolerated. Two patients complained of mild indigestion that did not require cessation of therapy.

**Conclusions:** Citrate supplementation with lemonade increased urinary citrate levels more than 2-fold without changing total urinary volume. Lemon juice, which contains nearly 5 times the concentration of citric acid compared to orange juice, is an inexpensive and well tolerated dietary source of citrate. Lemonade therapy may improve patient compliance, and may be useful as adjunctive treatment for patients with hypocitraturic calcium nephrolithiasis.

KEY WORDS: calcium, urinary calculi, diet, citrates

Hypocitraturia is a common etiology of recurrent calcium nephrolithiasis, with an incidence of 19 to 63%.<sup>1-3</sup> Citrate is a known inhibitor of calcium based stones. Its presence in urine decreases the saturation of calcium oxalate and calcium phosphate by forming soluble complexes with calcium, and by inhibiting crystal nucleation and growth.<sup>4</sup> Pharmacological supplementation with potassium citrate has been demonstrated to increase urinary citrate levels, and decrease urinary calcium excretion and relative saturation with respect to calcium oxalate.<sup>5-7</sup> Compared to conservative treatment with increased fluid intake and standard dietary modifications, the rate of new stone formation in patients with hypocitraturic calcium nephrolithiasis is significantly less with pharmacological potassium citrate therapy.<sup>6,8,9</sup>

Dietary recommendations in patients with calcium oxalate based stones include decreasing sodium intake, and limiting excessive oxalate and protein rich foods.<sup>10</sup> When hypocitraturia is noted on urinary biochemical profiles, addition of potassium citrate supplements is standard therapy. However, such therapy requires ingestion of as many as 12 tablets daily, or consumption of numerous crystal packages or liquid supplements 3 to 4 times per day. This regimen may dramatically decrease compliance and can impose a financial burden on the patient. Dietary citrate may be an adjunct or

even an alternative to pharmacological supplements, especially in patients who are poorly compliant with or intolerant of potassium citrate therapy.

Citrus fruits and juices represent a natural rich source of citrate, and can provide a dietary citrate load equivalent to that of routine potassium citrate supplements. Compared to the most commonly consumed citrus fruits, lemons contain among the greatest concentrations of citric acid, nearly 5 times that of oranges (table 1).<sup>11</sup> A half cup of pure lemon juice can provide a daily amount of citrate comparable to that of pharmacological therapy. We administered dietary citrate via a lemonade mixture to hypocitraturic calcium stone formers and evaluated the urinary biochemical effects.

TABLE 1. Chemical composition of citrus fruits

	Content/Kg.				
	Citric Acid (gm.)	Potassium (gm.)	Calcium (mg.)	Sodium (mg.)	Magnesium (mg.)
Orange	10.6	1.77	420	14	140
Grapefruit	13.7	1.80	180	16	130
Lemon	49.2	1.49	110	27	280
Raspberry	17.2	1.70	400	0	300
Pineapple	6.3	1.73	160	21	170
Cranberry	11.0	0.72	140	20	55

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## METHODS

The prospective study included 8 women and 4 men (mean age 55 years) with documented hypocitraturic calcium nephrolithiasis and 24-hour urinary citrate levels less than 320 mg. daily. Patients who were noncompliant with or intolerant of pharmacological citrate therapy were selected. No patient had active peptic ulcer disease or renal insufficiency. Patients were instructed not to change routine dietary habits except for lemonade ingestion. Before full metabolic evaluation, all patients were counseled to ingest adequate fluids to maintain a daily urine output of at least 2 l., and to adhere to a sodium and protein restricted diet. Patients who were previously taking pharmacological potassium citrate supplements discontinued their use more than 1 week before beginning lemonade therapy. Patients were instructed on home preparation of a standard daily lemonade mixture containing 120 cc (4 ounces) of reconstituted lemon juice (5.9 gm., or 84 mEq. citric acid) mixed with tap water to a total volume of 2 l. lemonade. Average cost of a 28 ounce bottle (1 week supply) was \$2. Sugar or sugar substitute was added to taste. This mixture was consumed at uniform intervals throughout each day for 1 week, with a recommendation of 3 glasses in the morning, 2 in the afternoon and 3 in the evening. On the last 2 days of the study period during lemonade consumption 24-hour urine samples were collected for biochemical analysis, and the results were compared to baseline values obtained before initiating the protocol. Urine samples were analyzed for total urinary excretion of citrate and total urinary volume in all 12 patients. In 10 of the 12 patients biochemical analyses also included urinary excretion of cal-

cium, oxalate and uric acid. Patients were surveyed at completion of the study to assess compliance and tolerance of the lemonade mixture. Results were expressed as mean plus or minus standard deviation. Statistical analyses were performed with paired Student's *t* tests.

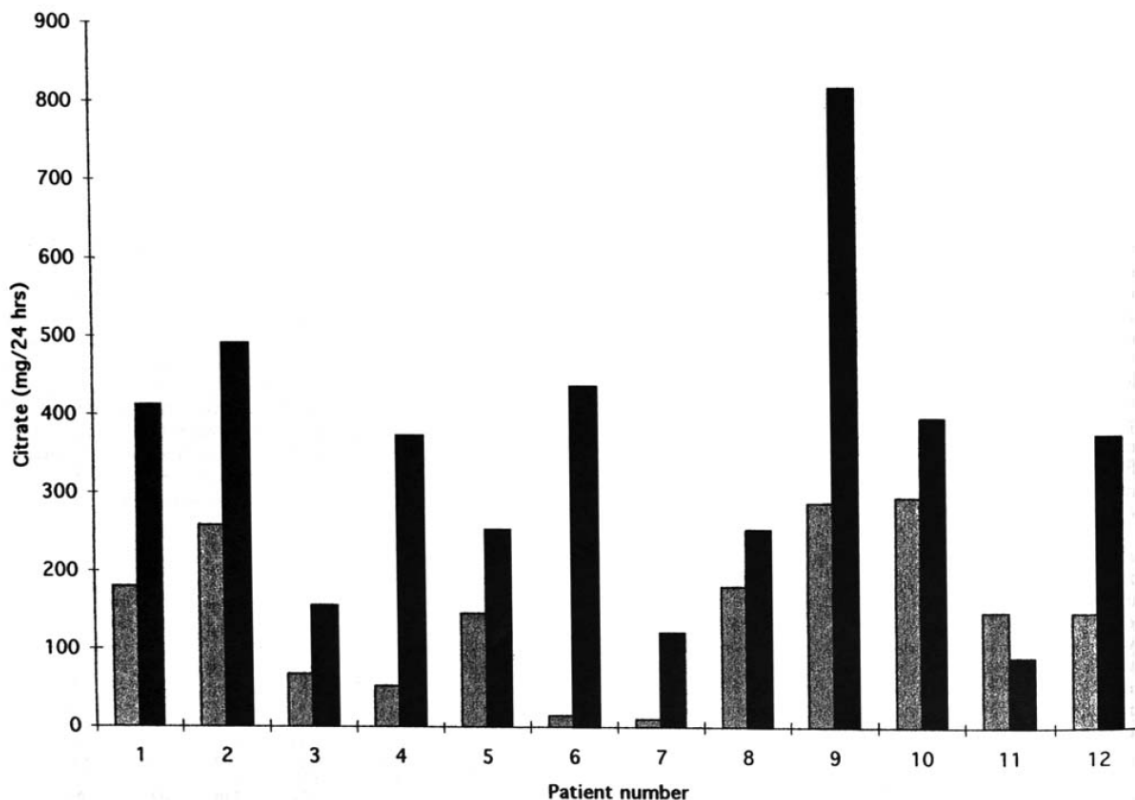
## RESULTS

Dietary citrate in the form of lemonade was well tolerated. Of 12 patients 2 complained of mild indigestion that did not require cessation of therapy. The figure shows the increase in urinary citrate levels for each patient while on dietary citrate. Of the 12 patients 11 demonstrated a mean increase in urinary citrate excretion of 204 mg. per day ( $p < 0.001$ ). Daily citrate excretion increased into the normal range of greater than 320 mg. daily in 7 patients.

Average 24-hour urinary excretion of citrate, calcium, oxalate and uric acid is shown in table 2. Mean daily urinary citrate excretion increased from 142 mg. at baseline to 346 mg. during lemonade consumption. Calcium excretion decreased in 8 of the 10 patients analyzed by an average of 39 mg. daily with lemonade therapy, although this change was not statistically significant. There was no significant change in oxalate or uric acid excretion. Total urinary volumes were similar before and while on lemonade therapy.

## DISCUSSION

The primary goal of treating hypocitraturic calcium nephrolithiasis is to increase 24-hour urinary citrate excretion to greater than 320 mg. Patients frequently ask how they can



Urinary citrate excretion (24-hour) for each patient before (□) and during (■) lemonade therapy

TABLE 2. Urine biochemistry

Daily Urinary Excretion	Mean $\pm$ SD	
	Before Lemonade	During Lemonade
Citrate (mg.)	142 $\pm$ 99	346 $\pm$ 197*
Calcium (mg.)	131 $\pm$ 119	92 $\pm$ 78
Oxalate (mg.)	53 $\pm$ 33	42 $\pm$ 12
Uric acid (mg.)	420 $\pm$ 153	436 $\pm$ 128
Vol. (l.)	2.7 $\pm$ 2.5	2.9 $\pm$ 2.4

\*  $p < 0.001$ .

alter their diet to help prevent recurrent urinary stones. Routine dietary modifications for hypocitraturic calcium nephrolithiasis have included sodium restriction, decreased overall protein intake and increased fluid ingestion to maintain a urinary specific gravity of less than 1.010 or to achieve a daily urine output of greater than 2 l.<sup>12</sup> There is a need to identify dietary modifications to help patients decrease stone recurrence rates. In this manner patients can become actively involved in treatment without the social stigmata of prescribed pharmacological therapy. This regimen hopefully will help increase patient compliance with and acceptance of potential lifelong therapy.

Patients with documented hypocitraturia (less than 320 mg.) are routinely treated with pharmacological citrate. Numerous studies have demonstrated the biochemical benefit of oral potassium citrate supplementation in elevating urinary citrate levels.<sup>4</sup> Other studies have shown that potassium citrate can decrease calcium excretion, increase urinary pH and decrease indexes of saturation with respect to calcium oxalate.<sup>5-7</sup> While the clinical relevance of hypocitraturia is well appreciated by the clinician, saturation indexes are not routinely used to direct clinical therapy. Clinical success with pharmacological citrate supplementation is determined by normalization of urinary citrate levels and a decrease in stone recurrence rates.

Pharmacological potassium citrate supplementation requires a rigorous schedule of numerous tablets or liquid supplements taken routinely 3 to 4 times daily. Patient compliance significantly decreases when medications are administered more than once daily.<sup>13</sup> Dropout rates attributable to the inconvenience of multi-tablet potassium citrate administration have surpassed 25% in long-term studies with 3 months to 3 years of followup.<sup>9, 14, 15</sup> Pharmacological citrate supplementation has been associated with gastrointestinal intolerance in 17 to 45% of patients on long-term therapy, resulting in decreased compliance and cessation of therapy.<sup>6, 9, 14, 15</sup>

Only 1 prior study evaluated the biochemical effects of dietary citrate in calcium stone formers.<sup>16</sup> In this study, orange juice was given to 8 normal subjects and 3 hypocitraturic patients. Results were pooled for all 11 patients, and average daily urinary citrate increased from 571 to 952 mg. during orange juice consumption. These results were nearly identical to those attained with pharmacological potassium citrate in the same 11 patients.

We administered dietary citrate in the form of lemonade to 12 patients with hypocitraturia. Compliance with and tolerance of the lemonade mixture were excellent in most patients who had prior difficulty complying with pharmacological citrate supplements. The daily consumption of lemonade resulted in increased urinary citrate levels by more than 2-fold without changing total urinary volume. More than half of the patients became normocitraturic while consuming lemonade.

Lemonade consumption also resulted in a trend towards decreased calcium excretion with no change in oxalate excretion. This finding differed from the biochemical changes observed during orange juice consumption in which there was no change in calcium excretion and a slight increase in oxalate excretion.<sup>16</sup> These differences probably reflect the greater calcium and ascorbic acid concentrations in orange

juice compared to our lemonade mixture. Ascorbic acid is metabolized in vivo to oxalate.

Although urinary pH was not measured in our study, one would not expect a significant alkali load with lemonade due to the small amount of potassium and other cations in the lemonade mixture. Such cations would promote urinary alkalization and further increase urinary citrate excretion. The citraturic action of dietary lemonade predominantly results from absorbed citrate that escapes metabolic degradation in vivo and is excreted unchanged by the kidney.<sup>17</sup>

## CONCLUSIONS

Lemonade therapy delivers a high citric acid load resulting in elevated urinary citrate levels. It is well tolerated, well accepted and an inexpensive form of treatment in hypocitraturic calcium stone formers. Lemonade may supplement or even replace conventional pharmacological therapy, especially in patients who are poorly compliant with or unable to tolerate pharmacological potassium citrate.

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