

## Long-Term Lemonade Based Dietary Manipulation in Patients With Hypocitraturic Nephrolithiasis

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**Purpose:** Citrus fruits and juices are a known natural source of dietary citrate. Of all the citrus juices, lemon juice appears to have the highest concentration of citrate. Therefore, lemonade therapy has been proposed as a potential treatment for patients with hypocitraturia. We retrospectively evaluated the impact of long-term lemonade therapy on urinary metabolic parameters and stone formation in patients with hypocitraturic nephrolithiasis.

**Materials and Methods:** A total of 32 patients were identified as being on long-term lemonade therapy for hypocitraturic nephrolithiasis. The 11 patients on lemonade therapy who met the entrance criteria for evaluation were compared to an age and sex matched control group of patients treated with oral slow release potassium citrate. Pre-therapy and post-therapy urinary parameters were recorded for both groups. The effect of lemonade therapy on stone burden and stone formation rate was calculated. New stone formation was defined as passage, surgical removal or appearance of new stones, or an increase in the size of existing stones on radiographic imaging.

**Results:** Four males and 7 females (mean age 52.7 years) were treated with lemonade therapy for a mean of 44.4 months. The control group consisted of 4 males and 7 females (mean age 54.5 years) treated with potassium citrate for a mean of 42.5 months. Of the 11 patients on lemonade 10 demonstrated increased urinary citrate levels (mean increase +383 mg per day,  $p < 0.05$ ). All potassium citrate therapy subjects demonstrated an increase in urinary citrate (mean increase +482 mg per day,  $p < 0.0001$ ). Mean pretreatment and posttreatment stone burden in the lemonade group was 37.2 and 30.4 mm<sup>2</sup>, respectively ( $p > 0.05$ ). During lemonade therapy the stone formation rate decreased from 1.00 to 0.13 stones per patient per year ( $p > 0.05$ ).

**Conclusions:** Due to its significant citraturic effect, lemonade therapy appears to be a reasonable alternative for patients with hypocitraturia who cannot tolerate first line therapy. Future study in the form of a prospective, randomized trial is needed to validate these findings.

*Key Words: nephrolithiasis, calculi, citric acid*

**H**ypocitraturia is a common metabolic defect found in patients with recurrent calcium nephrolithiasis. Although potassium citrate is widely accepted as first line therapy for the treatment of hypocitraturic nephrolithiasis, compliance with this treatment may be difficult in some patients due to gastrointestinal disturbances and/or financial burden. Moreover, some patients simply prefer nonprescription therapy.

Citrus fruits and juices are a natural dietary source of citrate and may represent an alternative to pharmacological therapy. Lemonade therapy has been proposed as an alternative to potassium citrate for treatment of hypocitraturia in recurrent stone formers. Herein we retrospectively evaluate the impact of long-term lemonade therapy on metabolic parameters in patients with mild to moderate hypocitraturia.

We also investigate the effect of lemonade therapy on stone burden and SFR in these patients.

### METHODS

#### Study Population

The records of patients seen at the Duke Comprehensive Kidney Stone Center between January 1995 and October 2003 were identified by a single reviewer (DEK). A diagnosis of hypocitraturic nephrolithiasis, availability of pretreatment and posttreatment 24-hour urinary profiles, and minimum of 6 months of followup were required for inclusion in the study. Hypocitraturia was defined as a urinary citrate level of less than 500 mg per day. The presence of concomitant metabolic disorders did not prompt exclusion from the study.

Lemonade therapy consisted of 120 ml concentrated lemon juice (5.9 gm citric acid) mixed with 2 l water con-

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\* Nothing to disclose.

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sumed throughout each day. A total of 32 patients on lemonade therapy were identified. Of the patients on lemonade therapy 5 were excluded due to concurrent potassium citrate therapy. An additional 12 subjects were excluded due to lack of available pre-therapy 24-hour urinary parameters (2) or incomplete followup (10). Of the remaining 15 patients 11 had pretreatment urinary citrate levels of less than 500 mg per day and were included in the review.

An age and sex matched control group of patients treated with oral potassium citrate was identified (11). Patients in the control group were treated with oral slow-release potassium citrate 20 mEq twice daily for the entire study period. Pre-therapy and post-therapy 24-hour urinary metabolic parameters (total volume, pH, citrate, magnesium, calcium, sodium, uric acid and oxalate) for subjects in both cohorts were recorded. The pre-therapy and post-therapy ion activity product of calcium oxalate was calculated for each subject using the modified formula reported by Tiselius.<sup>1</sup> All patients in both cohorts were advised to increase urinary volumes to more than 2,500 ml per day, and limit intake of salt, animal protein and oxalate rich foods. Patients with hypercalciuria were instructed to moderate intake of calcium and/or treated with thiazide diuretics.

### Statistical Analyses

The primary outcome measure was mean change in urinary citrate level. This value was assessed with the paired Student's t test using SPSS® version 12.0.1. Mean changes in remaining urinary parameters and calcium oxalate ion activity product were also examined and compared using the paired Student's t test. Change in stone burden and SFR within the lemonade therapy cohort was analyzed using the paired Student's t test. Difference in mean urinary citrate increase between the lemonade and potassium citrate groups was determined using the nonpaired Student's t test.

### Stone Burden

To assess the effect of lemonade on stone burden, pretreatment and posttreatment abdominal x-rays with tomograms or noncontrast abdominal/pelvic computerized tomography for each subject on lemonade therapy were reviewed by 2 observers (GEH and NJF). Reviewers were blinded to the date of the imaging study. The area (mm<sup>2</sup>) of each stone was determined by multiplying the maximum length and width of each fragment. Overall stone burden was determined by summing the areas of the individual fragments.

Change in SFR was determined for each patient on lemonade therapy. The pre-therapy and post-therapy SFR was

based on history by determining the number of stones formed and dividing by the duration of treatment, in years. New stone formation was defined as spontaneous passage, surgical removal, or appearance of new stones on radiographic imaging. Increase in size of existing stones on imaging studies was also defined as new stone formation.

## RESULTS

### Patient Population

In terms of demographic information the lemonade therapy group consisted of 4 males and 7 females (mean age 52.7 years, range 21 to 77). Mean treatment duration for the cohort was 44.4 months (range 7 to 96 months, SD 30.8). Of 11 patients on lemonade therapy potassium citrate therapy failed in 5 (45%) due to gastrointestinal disturbances and/or poor compliance. The remaining 6 were placed on lemonade therapy due to financial constraints, or as conservative treatment of hypocitraturia. The potassium citrate cohort consisted of 4 males and 7 females (mean age 54.5 years, range 26 to 75). Mean treatment duration for this group was 42.5 months (range 15 to 110, SD 30.9). Mean pre-therapy urinary citrate, patient age and length of followup for both cohorts were similar.

### Urinary Metabolic Parameters

Mean pre-therapy and post-therapy 24-hour urinary metabolic parameters are shown in the table. Of 11 patients on lemonade therapy 10 exhibited multiple metabolic abnormalities including hypocitraturia (11), low urinary volumes (8) and hypercalciuria (7). Of the 7 patients with hypercalciuria 3 were treated with thiazide diuretic therapy. Of 11 patients receiving lemonade 10 demonstrated an increase in urinary citrate levels. Mean urinary citrate increased from 350 to 733 mg per day (mean increase +383 mg per day, 95% CI 282 to 484,  $p < 0.05$ ). Of 11 patients in the potassium citrate control group 9 exhibited multiple metabolic abnormalities, including hypocitraturia, low urinary volumes (6), hypercalciuria (3), gouty diathesis (1) and hyperoxaluria (1). Of the 3 patients with hypercalciuria 2 were treated with a thiazide diuretic in addition to potassium citrate therapy. Mean urinary citrate level of the potassium citrate group increased from 349 to 831 mg per day (mean increase +482 mg, 95% CI 456 to 508,  $p < 0.0001$ ). The mean change in urinary citrate for the potassium citrate group was significantly higher than that of the lemonade group (482 and 383 mg per day, respectively,  $p < 0.05$ ). No statistically significant changes in mean volume, pH, calcium, sodium, uric acid and oxalate were observed in the lemonade group. Non-

<i>Pre-therapy and post-therapy 24-hour urine values</i>						
	Lemonade Mean (SD)			Potassium Citrate Mean (SD)		
	Pre-therapy	Post-therapy	Change	Pre-therapy	Post-therapy	Change
Vol (ml)	1,942 (817)	2,354 (471)	412 (771)	2,098 (804)	2,488 (820)	390 (1,031)
pH	6.1 (0.4)	6.2 (0.5)	0.1 (0.5)	6.3 (0.5)	6.9 (0.3)	0.6 (0.5)*
Calcium (mg/day)	211 (103)	219 (126)	8 (160)	187 (136)	173 (54)	-14 (124)
Sodium (mEq/day)	155 (69)	186 (67)	31 (84)	132 (62)	163 (71)	31 (41)
Uric acid (mg/day)	455 (154)	533 (188)	78 (152)	468 (199)	639 (209)	171 (184)*
Oxalate (mg/day)	27 (13)	28 (6)	1 (14)	28 (26)	35 (13)	7 (23)
Citrate (mg/day)	350 (109)	733 (160)	383 (136)*	349 (115)	831 (147)	482 (79)*

\* Paired Student's t test  $p < 0.05$ .

significant changes in volume, calcium, sodium and oxalate, as well as significant increases in pH and uric acid ( $p < 0.05$ ), were observed in the potassium citrate group.

A decrease in mean ion activity product for calcium oxalate was observed in both cohorts. Mean pretreatment and posttreatment ion activity product for the lemonade therapy group was 0.91 and 0.68, respectively while the potassium citrate cohort ion activity product was 0.71 and 0.61 ( $p > 0.05$ ).

### Stone Burden

Mean pretreatment and posttreatment stone burden was 37.2 and 30.4 mm<sup>2</sup>, respectively ( $p > 0.05$ ). During lemonade therapy the mean SFR decreased from a pretreatment level of 1.00 to 0.13 stones per patient per year ( $p > 0.05$ ). None of the patients on lemonade therapy had progression of stone burden requiring surgical intervention.

### DISCUSSION

Citrate is a known inhibitor of stone crystallization in patients with hypocitraturic calcium oxalate nephrolithiasis. By forming a soluble complex with urinary calcium, citrate helps to prevent a supersaturated state, which may lead to formation of calcium stones. Citrate also delivers a urinary alkali load through its conversion to bicarbonate. Increased urinary pH induces an additional citraturic response by slowing renal citrate metabolism and impairing citrate reabsorption.<sup>2</sup> While several options exist for patients requiring pharmacological citrate supplementation, potassium citrate is widely accepted as the standard therapy for hypocitraturic nephrolithiasis, as potassium citrate has been shown to decrease the rate of stone formation when compared to conservative therapy.<sup>3</sup>

While potassium citrate therapy is a first line option for prophylaxis of recurrent calcium nephrolithiasis in hypocitraturic stone formers, some patients prefer nonpharmacological intervention. Citrus fruits and juices are a known natural source of dietary citrate, and several studies have investigated the impact of orange and grapefruit juice on urinary parameters.<sup>4-7</sup> In one such investigation 11 subjects were sequentially administered a 7-day course of potassium citrate or orange juice with 3 days of rest between each treatment phase.<sup>4</sup> Potassium citrate and orange juice resulted in an average increase in urinary citrate of 373 and 381 mg per day, respectively. Compared to potassium citrate, orange juice elicited a similar increase in urinary pH (from 5.71 to 6.48 and 6.75, respectively). Of note, the authors also observed an increase in urinary oxalate and no change in calcium excretion with orange juice administration. This study concluded that while orange juice may be beneficial in the prevention of calcareous and uric acid nephrolithiasis, it is ineffective in decreasing urinary saturation of calcium oxalate.

In another investigation the impact of fruit juice on urinary metabolic profiles, administered as orange, grapefruit or apple juice to 9 healthy female subjects was studied during 2 days.<sup>5</sup> The authors observed an increase in pH and citrate excretion with each of the 3 juices, but the decrease in relative supersaturation of calcium oxalate crystallization was significant only for grapefruit juice.<sup>5</sup>

Two additional studies have examined the impact of grapefruit juice on urinary excretion of citrate and addi-

tional risk factors for stone formation. In 1 investigation grapefruit juice was administered to 10 healthy subjects for a 7-day period, eliciting an increase in mean oxalate and citrate excretion when compared to the control period.<sup>6</sup> No net change in the supersaturation of calcium oxalate, calcium phosphate, or uric acid was observed. An additional study evaluated the impact of a soft drink containing grapefruit juice on 7 healthy subjects, and found that grapefruit juice significantly increased urinary volume, excretion of citrate, calcium and magnesium compared to mineral water.<sup>7</sup> The results suggest while grapefruit juice may represent an alternative to potassium citrate for the prevention of calcium nephrolithiasis, a reduced sugar content is needed to avoid an increase in urinary calcium caused by sugar supplementation.

Although the preceding studies have examined the effects of orange, grapefruit and apple juice on urinary parameters, lemon juice appears to have the highest concentration of citrate of all citrus juices. Yet only 2 previous studies have investigated lemonade therapy as a potential treatment for hypocitraturic nephrolithiasis.<sup>8,9</sup> In the first such study investigators prospectively examined the short-term effects of lemonade on the urinary parameters of 12 patients with hypocitraturia who were previously noncompliant with pharmacological citrate therapy.<sup>8</sup> After 7 days of treatment, 11 of 12 patients showed a mean increase in urinary citrate of 204 mg per day ( $p < 0.001$ ). Pretreatment and posttreatment urinary volumes and oxalate excretion were unchanged, while urinary calcium excretion decreased an average of 39 mg per day. The study concluded that lemon juice is an inexpensive and well tolerated dietary source of citrate that may improve patient compliance and be used as adjunctive therapy in patients with hypocitraturia. While these results in a prospective setting were encouraging, the investigation was limited by short-term followup of only 7 days, thereby preventing any analysis of the impact of lemonade therapy on long-term urinary parameters, as well as stone formation.

Recently experience with lemonade monotherapy in 63 patients was compared to the results of 37 patients on potassium citrate and lemonade.<sup>9</sup> Patients on lemonade alone sustained a higher mean urinary volume and achieved a higher post-therapy urinary citrate than those patients on potassium citrate plus lemonade (2.34 vs 2.19 l and 770 vs 559 mg per day, respectively). However, the mean increases in urinary citrate from baseline levels were statistically significant only in the potassium citrate cohort. The effect of lemonade therapy on stone formation was not examined.

To our knowledge the current study is the first to evaluate the long-term effects of lemonade therapy on 24-hour urinary metabolic parameters, stone burden and stone formation rates. These results demonstrate the long-term citraturic action of lemonade therapy, as 11 of 12 patients on lemonade therapy exhibited clinically and statistically significant increases in citrate levels over a sustained period of time. Additionally, no significant change in mean urinary volume, calcium, sodium and uric acid in the lemonade therapy cohort was observed, which is in accordance with the previously performed short-term study.<sup>8</sup> An increase in urinary oxalate, a risk seen with orange juice administration, was not observed in our patients on lemonade therapy.

While improvement in 24-hour urinary citrate is beneficial, the primary goal of any therapy is the correction of

underlying metabolic abnormalities and, ultimately, the prevention of new stone formation. Therefore, we sought to evaluate the effect of lemonade therapy on long-term stone formation and stone burden. While the lemonade therapy cohort experienced a decrease in stone burden and SFR, these reductions did not achieve statistical significance. However, the observed impact on stone formation appeared to be clinically significant, as none of the 11 patients on long-term therapy required surgical intervention for progression of stone disease during the almost 4 years of followup. We believe that statistical significance with regard to stone formation might have been achieved with a larger cohort of patients.

Nonetheless, given the lack of disease progression and the significant citraturic response of patients on lemonade therapy, clinicians may consider lemonade as a potential long-term alternative for potassium citrate in patients with mild to moderate hypocitraturic nephrolithiasis. Patient compliance may also increase with long-term lemonade therapy compared to traditional pharmacological treatment. To our knowledge none of the patients in whom lemonade therapy was initiated discontinued therapy. However, it is unknown whether the patients lost to followup did not return because they successfully continued on lemonade therapy without recurrence of stone disease, or stopped lemonade therapy secondary to side effects but simply failed to return to clinic to seek alternative treatment options.

Our data suggest a role for lemonade therapy in select patients with hypocitraturia. However, it is important to note that in the current study patients treated with slow release potassium citrate demonstrated a significantly greater citraturic response than with lemonade therapy while increasing urinary pH, thereby increasing dissociation of uric acid and potentially inhibiting the formation of uric acid stones.<sup>10</sup> Whether the greater increase in urinary citrate seen in the potassium citrate cohort is of clinical significance remains unknown. The citraturic action of potassium citrate was once attributed solely to the alkali load delivered by oxidation of citrate to bicarbonate. Potassium citrate is now known to work not only through oxidation of citrate to bicarbonate but also through the direct renal excretion of citrate.<sup>10-14</sup> In contrast, lemonade therapy does not deliver a urinary alkali load due to the low pH of lemon juice. Rather, it induces a citraturic response through the renal excretion of nonmetabolized citrate alone, which may explain the lemonade therapy cohort's comparatively attenuated response.<sup>15-17</sup>

The findings of the current long-term study support the previously postulated mechanisms of action for citric acid, as lemonade therapy effectively increased mean urinary citrate without altering urinary pH. Given the lack of alkali load of lemon juice, clinicians should be aware that lemonade therapy would be of limited benefit in treating patients with uric acid nephrolithiasis.

This study is hindered by the limitations inherent to a retrospective review. While 32 patients on lemonade therapy at our institution were identified, only 11 were included in the study, thereby decreasing the precision of our treatment effect. However, by excluding patients with incomplete followup and concurrent potassium citrate therapy, we believe that confounding factors were minimized while maintaining statistical power. Additionally, the ability to extrapolate this study's findings to the general population may be limited because each cohort included more women than men and study subjects were selected from patients treated at a tertiary referral facility with a dedicated comprehensive kidney stone center. Finally, clinicians should note that this study used a conservative definition of hypocitraturia (less than 500 mg per day) because most patients placed on lemonade therapy at our institution were mildly hypocitraturic, prompting conservative treatment. It remains unknown whether patients with serious hypocitraturia would exhibit a similar response to lemonade therapy.

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## CONCLUSIONS

Due to its significant citraturic effect, lemonade therapy appears to be a reasonable alternative for patients with hypocitraturia who cannot tolerate first line therapy. Future study in the form of a prospective, randomized trial is needed to validate these findings.

### Abbreviations and Acronyms

SFR = stone formation rate

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#### EDITORIAL COMMENT

The authors address an important clinical issue in the medical treatment of calcium stone formers. As noted, citrate is a potent urinary crystal inhibitor, and pharmaceutical agents that increase urinary citrate are generally first line therapy for hypocitraturia. However, inherent drawbacks to this strategy include patient compliance with medications, gastrointestinal side effects and cost. Another concern is that medications that increase urinary citrate also increase uri-

nary pH, potentially promoting the precipitation of calcium phosphate crystals in susceptible individuals.<sup>1</sup>

Nutrition therapy for hypocitraturia, emphasizing citrate based fluid replacement, and alkaline ash fruits and vegetables rich in citric acid, could be a viable alternative or adjunct to pharmacological therapy.<sup>2</sup> In this retrospective study Kang et al identified increased urinary citrate concentrations without a change in pH in patients treated with lemonade therapy. Larger, prospective clinical studies are warranted to confirm these results and to identify more precise target urinary citrate concentrations.

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