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Long-Term Effects of Lemonade Therapy on Hypocitraturic Nephrolithiasis and Stone Recurrence: A Mini Review

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Abstract

Background: We sought to assess the strength of the evidence for long-term lemonade therapy on urinary citrate excretion and stone formation in patients with hypocitraturic nephrolithiasis.

Context of the study: A literature search was conducted via PubMed (1970–June 2015) using the key terms "lemonade" and "hypocitraturic nephrolithiasis," as well as the Medical Subject Headings "medical therapy," "lemon juice," and "potassium citrate". We included peer-reviewed articles with English abstracts if they reported a study of hypocitraturic nephrolithiasis that compared consumption of lemonade with pharmacological agents available on the market. Reasons for excluding potentially relevant articles included the lack of a study outcome of direct relevance to hypocitraturic nephrolithiasis and the absence of a direct comparison of lemonade with pharmacological agents.

Results: From a total of 339 articles, we identified 51 potentially relevant studies. An examination of the full text of these articles resulted in the exclusion of 45 studies that did not meet the inclusion criteria. A final total of six publications were included in the review. One prospective study and five randomized controlled trials of 226 patients with hypocitraturic nephrolithiasis that compared lemonade with placebos or other regimens were included.

Main findings: From this review of currently available published literature, evidence is lacking that lemonade therapy is effective for the prevention of hypocitraturic nephrolithiasis, although many studies show that lemonade can increase urinary citrate levels.

Conclusion: There is a lack of evidence supporting lemonade therapy in the prevention of hypocitraturic nephrolithiasis.

Keywords: Lemonade; Hypocitraturic; Nephrolithiasis

Introduction

Nephrolithiasis is a highly prevalent, painful, and costly disease pattern that is further aggravated by a high recurrence rate [1-4]. Fortunately, a number of drugs [5] and certain dietary measures [6,7] have been shown in randomized trials to reduce the rate of stone recurrence. Indeed, a meta-analysis of randomized medical therapy trials showed a 22.6% risk reduction in stone recurrence rates with the initiation of drug and dietary therapy [5]. Despite these effective treatments, however, the disease showed no signs of abating, in part because of poor patient compliance with prescribed drug therapies.

Low urinary citrate excretion is a known risk factor for the development of kidney stones [8]. Hypocitraturia, generally defined as urinary citrate excretion less than 320 mg (1.67 mmol) per day for adults [9], is a common metabolic abnormality in stone formers, occurring in 20% to 60% of cases [1,8,10-13]. Citrate is a known inhibitor of stone formation, working through a variety of mechanisms. In the renal tubule, citrate complexes with calcium, increasing its solubility and reducing the concentration of free calcium in the urine. This calcium–citrate complex limits calcium supersaturation and prevents nucleation of both calcium oxalate and calcium phosphate, at least partly through interactions with Tamm-Horsfall protein [14,15]. Additionally, citrate prevents crystal agglomeration and growth through its ability to bind to the crystal's surface and may also prevent adhesion of calcium oxalate to renal epithelial cells [16-18]. Hypocitraturia may be corrected with dietary modifications and the administration of citrate preparations or other forms of alkali therapy. Citrate excretion is linked to urinary pH and thus may influence the generation of a number of types of stones.

Hypocitraturia is associated with recurrent calcium nephrolithiasis [19]. Although potassium citrate is widely accepted as first-line therapy for the treatment of hypocitraturic nephrolithiasis, compliance with this treatment may be difficult for some patients, owing to gastrointestinal disturbances and/or the financial burden of care. 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 the treatment of hypocitraturia in recurrent stone formers. We sought to assess the strength of the evidence of long-term lemonade therapy on urinary metabolic parameters and stone formation in patients with hypocitraturic nephrolithiasis.

Methods

A literature search was conducted via PubMed (1970–June 2015), using the key terms "lemonade" and "hypocitraturic nephrolithiasis,"

as well as the Medical Subject Headings "medical therapy," "potassium citrate," "lemon juice," "lemonade," and "hypocitraturic nephrolithiasis." We included peer-reviewed articles with English abstracts if they reported a study of hypocitraturic nephrolithiasis that compared consumption of lemonade with available pharmacological agents, such as potassium citrate 10 mEq.

Articles were excluded if they dealt with hypocitraturic nephrolithiasis unrelated to the consumption of lemonade, investigated animal trials, or were primarily concerned with the effects of citrus contaminant content.

From a total of 339 articles, we identified 51 potentially relevant studies. An examination of the full text of these articles resulted in the exclusion of 45 studies that did not meet the inclusion criteria. Reasons for excluding potentially relevant articles included the lack of a study outcome of direct relevance to hypocitraturic nephrolithiasis and the absence of a direct comparison of lemonade compared with pharmacological agents. A final total of six publications were included in the review [20-26]. One prospective study and five randomized controlled trials of 226 patients with hypocitraturic nephrolithiasis that compared lemonade with placebos or other regimens were included.

Results

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 [27]. Other studies have shown that potassium citrate can decrease calcium excretion, increase urinary pH, and decrease indexes of saturation with respect to calcium oxalate [28-30]. Clinical success with pharmacological citrate supplementation is determined by the 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 three to four times daily. Patient compliance significantly decreases when medications are administered more than once daily [31]. Dropout rates attributable to the inconvenience of multi-tablet potassium citrate administration have exceeded 25% in long-term studies with three months to three years of follow-up [32-34]. Pharmacological citrate supplementation has been associated with gastrointestinal intolerance in 17% to 45% of patients in long-term therapy, resulting in decreased compliance or cessation of therapy [29,32-34].

Although the above-mentioned studies have confirmed 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. The first prospective study was conducted by Seltzer et al. [27] in 1996. 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 120 mL of reconstituted lemon juice (5.9 gm citric acid) mixed with tap water to make up a total volume of 2 liters, and consumed at uniform intervals throughout the day. Urine specimens (24-hour) were obtained for biochemical analysis after six days of lemonade therapy and compared to pre-lemonade baseline values. 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 to 1 before versus 2.9 to 1 after). Seven of the 12 patients became normocitraturic while consuming lemonade. Urinary calcium excretion decreased by an average of 39 mg daily, while oxalate excretion was unchanged. Seltzer et al. concluded that citrate supplementation with lemonade increases urinary citrate levels more than twofold, without changing total urinary volume, may improve patient compliance, and may be useful as adjunctive treatment for patients with hypocitraturic calcium nephrolithiasis.

Three trials concluded that lemonade can increase urinary citrate levels and can thus be an alternative in the treatment of urinary calcium stones in patients with hypocitraturia. The associated data and changes in the urinary parameters in these trials are shown in (Table 1) [22,23].

A study conducted by Koff et al. [24] suggests that lemonade does not yield improvements in urinary citrate levels. A total of 21 stone-forming patients were treated with lemonade therapy and potassium citrate supplementation in a prospective cross-over trial. The baseline mean citrate level was 476 mg/day. After treatment with lemonade, the mean

	Patient No.	Treatment duration	Lemonade type	Citrate level(pre)	Citrate level(post)	Potassium level(pre)	Potassium level(post)	P
Seltzer MA et al.[20]	12	6 days	4 ounce in 2.0L	142 ± 99	346 ± 197			<0.001
Penniston KL et al.[21]	63	39 m	LT(4 ounce)	683 ± 41	(+)203 ± 45	62 ± 2.9	(+)10 ± 5.1	0.15
	37	41 m	LT+PC	364 ± 34	(+)346 ± 45	53 ± 3.8	(+)42 ± 6.9	<0.001
Aras B et al.[22]	10	3 m	Lemon juice 85 ml	122.6 ± 64.69	302.7 ± 75.14			0.003
	10	3 m	Potassium citrate 60 mEq	85.50 ± 44.21	324.70 ± 114.15			0.001
	10	3 m	water	102.70 ± 22.62	186.5 ± 68.92			0.001
Tosukhowong P et al.[23]	13	3 m	Lime powder 5 gm	56	270	25.2	49	0.002
	11	3 m	Potassium citrate 60 mEq	69.7	387.4	34.9	55.6	0.01
	7	3 m	placebo	49.8	70.7	29.3	41.1	0.091
Koff SG et al.[24]	21	5 d's, 2 w's cross over	Lemonade 65 mEq	476 ± 467	446 ± 376	53.4 ± 20.2	48.4 ± 18.8	
			Potassium citrate 65 mEq	476 ± 467	583 ± 430	53.4 ± 20.2	75.8 ± 20.0	
Kang DE et al.[25]	11	44.4 m	Lemonade 65 mEq	350(109)	733(160)	349(115)	831(147)	

Table 1: The associated data and changes in the urinary parameters in these are shown in trials.

citrate level decreased to 446 mg/day. Treatment with potassium citrate yielded a mean level of 583 mg/day. This improvement was statistically significant (P = 0.0015). For patients with documented hypocitraturia at baseline, none had an improvement of their citrate levels into the normal range during lemonade therapy; however, three hypocitraturic patients (27%) experienced improvements of their citrate levels into the normal range during potassium citrate therapy.

The most promising study was reported by Kang et al. [25]. Thirty-two patients were identified as being on long-term lemonade therapy for hypocitraturic nephrolithiasis. The 11 patients on lemonade therapy who met the criteria for evaluation were compared to an age- and sex-matched control group of patients treated with oral slow-release potassium citrate. Pre- and post-therapy urinary parameters were recorded for both groups. The effects of lemonade therapy on stone burden and stone formation rate were calculated. New stone formation was defined as the passage, surgical removal, or appearance of new stones, or an increase in the size of existing stones on radiographic imaging. Four males and seven females (mean age 52.7 years) were treated with lemonade therapy for a mean of 44.4 months. The control group consisted of four males and seven 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 post treatment stone burden in the lemonade group was 37.2 and 30.4 mm^2, respectively ($p < 0.05$). During lemonade therapy, the stone formation rate decreased from 1.00 to 0.13 stones per patient per year ($p < 0.05$).

Five studies have investigated lemonade therapy as a potential treatment for hypocitraturic nephrolithiasis. In these studies, the investigators prospectively examined the short-term effects of lemonade on the urinary parameters of 226 patients with hypocitraturia. After the treatment, the patients showed a mean increase in urinary citrate levels. Pretreatment and post treatment urinary volumes and oxalate excretion were unchanged. All the studies concluded that lemon juice is an inexpensive and well-tolerated dietary source of citrate that may improve patient compliance and can be used as adjunctive therapy in patients with hypocitraturia. While these results were encouraging, the investigation was limited by short-term follow-up, thereby preventing any analysis of the impact of lemonade therapy on long-term urinary parameters, as well as on stone formation.

Discussion

As to 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. However, it is unknown whether the patients lost to follow-up did not return because they continued on lemonade therapy successfully without the recurrence of stone disease, or stopped lemonade therapy due to side effects and simply failed to return to the clinic to seek alternative treatment options. To date, the evidence base of treatment with lemonade for hypocitraturic nephrolithiasis is small, although it is found that lemonade therapy elevates urinary citrate levels.

The primary goal of treating hypocitraturic calcium nephrolithiasis is to increase the 24-hour urinary citrate excretion to greater than 320 mg. Patients frequently ask how they can alter their diets 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 daily urine output of greater than 2 L [26]. Dietary modifications to help patients decrease stone recurrence rates should be identified, allowing patients to become actively involved in their treatment without the social stigma of prescribed pharmacological therapy. This regimen is likely to help increase patient compliance with and acceptance of potential lifelong therapy.

Although specialists fully understand the clinical relevance of hypocitraturia, they do not routinely use saturation indexes to direct therapy.

Conclusions

From this review of currently available published literature, evidence is lacking that lemonade therapy is effective in the prevention of hypocitraturic nephrolithiasis. However, many studies show that lemonade can increase urinary citrate levels. Lemonade therapy cannot replace the role of potassium citrate in the prevention of hypocitraturic nephrolithiasis. A future large-scale, long-term study using a prospective, randomized trial is needed to compare the clinical efficacy of lemonade and potassium citrate.

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Contributions

Research idea and study design: CJW, CSH, PCT; data acquisition: CJW, PCT, CHC, CSH, HWC; data analysis/interpretation: CJW, CSH, HWC, PCT, CHC; statistical analysis: CJW, CSH; supervision or mentorship: CJW. Each author contributed important intellectual content during the manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work will be appropriately investigated and resolved. CJW, PCT, CHC, CSH and HWC affirm that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies in the study as planned and registered have been explained.

The corresponding author affirms that there are no financial or commercial interests to declare and that the work has not already been published or submitted simultaneously to any other journal.

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