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## **Efficacy of Alkali Citrate Salts in the Prevention of Kidney Stone Formation**

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## **Abstract**

Kidney stones are a common urinary tract disorder with increasing prevalence in the United States and in the world. Medical therapy can be effective in preventing the recurrence of stones. Effective therapies include increasing fluid intake, dietary modification and pharmacologic manipulation of urinary chemistry. Among the few effective pharmacologic options is supplementation with citrate. Citrate in the urine antagonizes crystallization of calcium oxalate or phosphate, so that increasing urinary citrate excretion prevents kidney stone recurrence. In addition, the metabolism of citrate by the liver (and kidney) consumes a proton, equivalent to the generation of alkali, or bicarbonate. The result is an increase in bicarbonaturia and urine pH, a manipulation that effectively increases the solubility of uric acid and cystine. In this review, we survey the efficacy of alkali citrate salts, including sodium, potassium and magnesium citrate, to prevent stone recurrence. We limit our analysis to human studies that examined the effects of one or more of these citrate salts on kidney stone recurrence. We demonstrate that there is a consensus in the kidney stone literature regarding the efficacy of alkali citrate salts to reduce kidney stone recurrence. In addition, we review the ability of citrate supplementation to favorably alter urinary citrate excretion and pH, both of which are associated with prevention of kidney stones of varying composition.

## Introduction

Kidney stones are known to be one of the most common and painful urologic disorders. It is estimated that 11% of the US population will have at least one kidney stone in their lifetime.<sup>1</sup> Due to multiple factors, the prevalence of kidney stones is increasing. There also is a prodigious increased incidence of stones in women over the past 10 years.<sup>2</sup> Kidney stones are the most common urologic reason for Emergency Room visits in the US. Recent estimates place the annual health care costs (US) for this affliction to be as high as \$10 billion.<sup>1</sup> Unfortunately, the recurrence rate for kidney stones is 50% in 5 years and 80% in 20 years. Certain heritable traits also may contribute to kidney stones formation as family history of stones is associated with increased kidney stone risk.<sup>3</sup> Despite these facts, the majority of people with kidney stones do not receive appropriate information or guidance to prevent stone recurrence. The standard of care to prevent further stones are increased fluid intake, dietary modifications, and pharmacologic therapy with potassium citrate (K-Cit) and thiazides.<sup>4</sup> Proper implementation of these therapies can significantly decrease the incidence of recurrent stones.

Since 1985, K-Cit has been the cornerstone of pharmacologic intervention for kidney stone diathesis.<sup>5</sup> However, treatment with K-Cit is impaired by poor long-term compliance. This is secondary to significant gastrointestinal (GI) upset (most likely from the potassium component), difficulty swallowing the large pills, offensive taste to some, and expense.<sup>6</sup> Also, due to the potassium component, serum potassium levels need to be monitored routinely, adding both cost and inconvenience.

Citrate salts alter urine chemistry by increasing urinary citrate excretion and pH while having a variable effect to decrease urinary calcium excretion.<sup>7</sup> Increasing urinary citrate is recognized as an inhibitor of calcium-containing kidney stones, both calcium oxalate (CaOx) and calcium phosphate.<sup>8</sup> In addition, metabolism of citrate consumes a proton, equivalent to generating bicarbonate. The result is an increase in urinary pH, which causes dissociation of relatively insoluble uric acid to the urate anion, titrating the associated proton.<sup>9</sup> This effect

decreases uric acid supersaturation and thereby inhibits crystallization. The available citrate salt-containing products are relatively expensive and have increased in price. Most people find liquid forms of potassium citrate relatively unpalatable. The development of an inexpensive over-the-counter (OTC) product that combines the diverse, available citrate salts and delivers a therapeutic dose of alkali citrate while maintaining a favorable flavor profile could shift the paradigm of kidney stone management. The following article reviews and discusses the extensive literature of the role of alkali citrate to decrease kidney stone recurrence. This review does not include a review of alkali absorption by the intestine, citrate transport by the kidney, or the effects of citrate as an inhibitor of crystallization all of which have been detailed elsewhere.<sup>10</sup>

## **Methodology**

### Research Strategy

In this review, we sought to examine the totality of evidence regarding the efficacy of alkali citrate in the prevention of kidney stone formation in humans. We utilized the PubMed/Medline database of literature. First, we identified relevant keywords that describe the compounds of interest (e.g. alkali citrate, citric acid, sodium citrate, potassium citrate, magnesium citrate), keywords that identified relevant health conditions (nephrocalcinosis, nephrolithiasis, urinary stone disease, calculi, renal). We then conducted a literature search for combinations of keywords for the preparations and health conditions of interest. A list of the keyword combinations used is provided in Table 1.

### Study selection and inclusion/exclusion criteria

For each literature search, reviewers would filter relevant results from the information available from the abstract. The following criteria was used to filter relevant literature:

- a- Study is performed in humans
- b- Study measured the effect of at least one of the following compounds: magnesium, potassium or sodium citrate on kidney stone recurrence or urinary surrogate

- measurements for kidney stone formation (specifically urinary citrate levels, pH, or calcium oxalate supersaturation)
- c- Study is in English language

Following the initial screening and identification, the curated studies were then analyzed for data extraction. In addition to the studies obtained through the literature search, we have also identified several relevant studies through reviewing pertinent review articles and meta-analyses.

#### Data extraction:

189 potentially relevant papers were identified. Each one of these papers was systematically analyzed in order to:

- a- Identify whether the study was interventional or observational
- b- Identify which compounds the study investigated, at what dosage they were used, and the duration of treatment
- c- Identify the population that participated and the types of kidney stones the patients formed
- d- Evaluate the strength of the study
- e- Record any reported measurements of kidney stone recurrence or changes in urinary surrogated measurements
- f- Record any reports on treatment adverse effect

#### Evaluating the strength of studies:

When evaluating the strength of any given study, two criteria were considered:

- 1- Number of participants: greater than or equal to 15 per group was considered a sign of strength as this sample size would allow the study to capture the small effect size reported for the adverse side effects of citrate treatments

- 2- Comparison to a placebo group: studies were penalized in terms of strength if they did not compare the results of the citrate salt treatment to a placebo group or to a stable baseline

In the annotated bibliography, symbols were used to designate a study's strength. Studies that satisfied both above criteria were considered strong and marked with \*\*. Studies that satisfied only one of the above criteria, were considered to be of intermediate strength and were marked \*. Finally, studies that failed to satisfy both criteria were considered weak and not given a marker.

Secondary filtration of compiled literature:

Following the analysis of the compiled literature, some of the studies identified as relevant in the literature search were ultimately excluded from analysis in this review due to one or a combination of the following reasons:

- a- Study was published in another language even though the title and abstract are in English
- b- Manuscript could not be obtained
- c- Article is a review or meta-analysis
- d- Study did not measure the effects on the measurements relevant to this literature review
- e- Article is not a peer-reviewed study but simply just a comment or a response to another previously published study, such as an editorial or letter to the editor
- f- Study is performed *in vitro* and not in humans

Ultimately, of the 189 papers compiled in the literature search, only 113 were retained for analysis. A complete annotated bibliography of all the 189 papers is represented in the annotated bibliography supplemental table at the end of this report; and reasons for exclusion

during the secondary filtration process are outlined for papers which were excluded during the second round.

## Results

### Potassium Citrate

The pharmacologic standard of care for calcium, cystine, and uric acid stone formers is K-Cit. It has been widely evaluated for its safety and efficacy to improve urinary chemistries in many clinical trials, where collectively, 412 healthy participants and 4720 patients with kidney stones have been evaluated.<sup>7,11-71</sup> Improved urinary chemistries using K-Cit were observed at a doses ranging from 20 to 100 mEq daily. In some active stone forming patients, K-Cit was used in combination with thiazides or allopurinol.<sup>19,25,27,40,44,58,64,72,73</sup> The efficacy of K-Cit to prevent kidney stones has been confirmed in clinical studies which include imaging results. With K-Cit treatments, 67 to 100% of stone forming patients had achieved remission or reduced the formation rate of kidney stones.<sup>5,12,22,27,36,37,45,57,64,66,68,69,71,74</sup> K-Cit has been shown to increase urinary citrate levels by 23% to 586% from baseline levels.<sup>5,7,11,12,15,16,21,22,27,29,31,33-35,37,44,45,47,51,54,55,60,64-66,68-70,75-81</sup> Studies have also shown an increase in urine pH of 0.3 to 1.3 over baseline for patients taking K-Cit.<sup>5,7,15,16,21,22,27-31,33-36,42,44,45,47,55,60,64-66,68-71,75-77,79-82</sup> Further improvement of urine chemistries in kidney stones formers included decreased urinary calcium levels by 5% to 53% from baseline and reduced CaOx saturation by up to 40%.<sup>7,28,32,33,36,44,45,51,55,64,65,68-70,76-78,80-83</sup> Although efficacious, K-Cit use has limited long term compliance. Investigators report that 6% to 14% of clinical study participants have complained about difficulty swallowing large pills, the offensive taste of K-Cit liquid, and the gastrointestinal distress caused by, most likely, the potassium component.<sup>20,37,43,57,84</sup> These gastrointestinal side effects are more pronounced in patients who suffer from irritable bowel syndrome or inflammatory bowel disease, who have kidney stones because chronic diarrhea leads to low urine volume, hypocitraturia, and low urine pH. K-Cit use requires physicians to monitor serum

potassium levels, which introduces additional cost. This issue is more marked in patients taking angiotensin converting enzyme inhibitors and angiotensin receptor blockers, drugs used frequently in patients with diabetes and hypertension. Diabetics have an increased rate of uric acid stones due to the “unduly acid urine pH” associated with insulin resistance.<sup>85</sup> Because of these adverse effects and compliance issues, researchers have studied combinations of various citrate salts to improve efficacy and compliance.

### Combinations and Variations of Alkali Citrate

Investigations of combinations and variations of citrate salts to attempt to mitigate the adverse effects of K-Cit have been conducted for over 2 decades; 15 studies included 506 participants.<sup>11,16,32,86-97</sup> Studies to evaluate the synergistic action of various citrate salts have also been done.<sup>95</sup> Combinations of K-Cit, sodium citrate and magnesium citrate have emerged in the literature. The use of magnesium as a stone preventive derives from its ability to serve as a binder of oxalate, both diminishing absorption of oxalate in the intestine, and binding to it in urine to prevent its binding to oxalate. Sodium citrate may be disadvantaged as significant increases in sodium excretion may result in increased urinary calcium excretion.

One influential study randomized 64 calcium stone formers to K-Cit/magnesium citrate and demonstrated that the combination of K-Cit and magnesium citrate reduced kidney stone recurrence by 85% in calcium stone formers over a 3 year period.<sup>90</sup> New calculi formed in 63.6% of subjects receiving placebo and in 12.9% of subjects receiving potassium-magnesium citrate. Urine citrate excretion increased from 587 to 769 mg per day, while pH changed from 6.01 to 6.29 in 24-hour urine collections, while no statistically significant changes occurred in the placebo group. This combination of citrate alkali was never produced commercially. Of importance, the gastrointestinal side effects of the K-Cit/magnesium citrate combination was not significantly different from placebo. The benefit was seen in patients who did not have hypocitraturia at baseline. Urine oxalate excretion was not favorably affected.

One study with 9 participants compared K-Cit with sodium citrate with and without magnesium oxide or placebo. Another study with 58 participants compared K-Cit/magnesium citrate/sodium citrate to placebo. In a study of patients with recurrent calcium urolithiasis, potassium/sodium/magnesium citrate significantly reduced crystal diameter by 17% compared to control. The beneficial effect of the addition of magnesium-containing citrate salts on urine chemistries was consistent across all of these studies. The pH value of urine increased 1.5 to 26% in the treatment groups while placebo groups showed no significant change in pH. Magnesium citrate significantly increased levels of urine citrate 19.4% to 101% while placebo groups had no change in citrate levels. Also of benefit, treatment groups experienced some reduction in urinary calcium and a 19% to 166% decrease in urinary oxalate. Two of the 15 studies (126 participants) evaluated side effects from combination alkali citrate treatment. One long term study of patients with recurrent kidney stones reported 25.8% of the citrate treatment group experienced more than slight gastrointestinal issues versus 15% of the placebo group. A study comparing K-Cit/magnesium citrate versus potassium chloride for treatment of thiazide-induced hypokalemia, the K-Cit/magnesium citrate combination was slightly better, probably because of the effect of magnesium on renal potassium excretion. There were no significant differences in frequency or severity of gastrointestinal symptoms.<sup>86</sup> Dietary magnesium deficiency is a known risk factor for urolithiasis.

Sodium citrate is another citrate salt that has been shown to be efficacious for prevention of kidney stones. Its safety and efficacy on improving urinary chemistries has been confirmed in clinical trials with at least 22 healthy participants and 60 patients with kidney stones.<sup>13,23</sup> Reported effective doses of sodium citrate are in the range of citrate from 60 to 80 mEq daily. Within the effective dosing range, sodium citrate has been shown to increase urinary citrate levels by 100% to 337% from the baseline levels.<sup>13</sup> Studies have also shown an increase in urine pH of 0.3 to 1.4 over baseline for patients taking sodium citrate.<sup>13</sup> Furthermore, significant reduction of urinary calcium levels by up to 10% from baseline and CaOx saturation

ratio by up to 41% with sodium citrate treatments are also reported.<sup>13</sup> No side effect due to sodium citrate treatments is reported in these clinical trials. In addition to sodium citrate alone, treatments with potassium/citrate citrate combination have also been widely studied for prevention of kidney stones. Its safety and efficacy on improving urinary chemistries has been confirmed in clinical trials with at least 214 healthy participants and 832 patients with kidney stones.<sup>30,56,67,98-106</sup> Reported effective doses of potassium/sodium citrate are in the range of citrate from 42 to 60 mEq daily. Potassium/sodium citrate has been shown to increase urinary citrate levels by 16% to 238% from the baseline levels.<sup>50,99,101,102,104,106-109</sup> Studies have also shown an increase in urine pH of 0.5 to 0.9 over baseline for patients taking potassium/sodium citrate.<sup>99,102,107</sup> Potassium/sodium citrate has shown further improvements on urinary chemistries, including significant reduction of urinary calcium by 16% to 22% from baseline as well as the decline in CaOx saturation ratio by up to 32% from baseline.<sup>56,99,105,106</sup> The efficacy of potassium/sodium citrate in kidney stones formers has also been confirmed with imaging results, where 31% to 88% patients have achieved disease remission or have the rate of kidney stones formation reduced.<sup>67,98,100,105,109</sup> A clinical study pointed out that kidney stones remission was greatly affected by long term compliance. In a 3-year window, 57% of patients had kidney stone remission, while in a 6-year window, only 38% of this population had kidney stone remission.<sup>98</sup> Therefore, in order to address the issue of poor long-term compliance, more options for kidney stones prevention are needed. Also, due to sodium's propensity to increase urine calcium, the amount of sodium citrate in a formulation of citrate salts must also be limited and therefore a formulation with citrate salt combination will be more favorable.

### Citrus juices

While citrate salts are a common pharmacological and widely accepted treatment for kidney stones, the side effects and cost often prohibit long term use in many patients. Therefore, consumption of citrus fruit juices has been proposed as a natural alternative intervention in the management of recurrent calcium containing stones.<sup>20,79,80,102,110-118</sup> Although

multiple studies have shown an increase in urinary citrate with this intervention, there is no standard amount of citrate that is recommended. Of the citrus fruit juices, lemon juice has the highest concentration of citric acid.<sup>119</sup> The first lemonade study showed significant increases in urinary citrate in 9 known hypocitraturic stone formers.<sup>114</sup> It was felt that lemon juice, with its significant citric acid content, could be used in patients with calcium nephrolithiasis who were intolerant to or unable to afford K-Cit. Another study compared K-Cit supplementation to that of orange juice in 8 healthy and 3 hypocitraturic patients.<sup>77</sup> The orange juice did increase both urinary citrate and pH, similar to the K-Cit, but the orange juice also increased urinary oxalate. Therefore, there was not a decrease in CaOx saturation, making orange juice therapy of limited use in comparison. In another study, orange juice was superior to lemon juice in alkalinizing and increasing urine citrate.<sup>120</sup> Another study looking at the long-term effectiveness of lemonade therapy in hypocitraturic patients showed a decrease in stone formation rate from 1.0 to 0.13 stones per patient per year<sup>113</sup>. Grapefruit juice increased urinary citrate but oxalate as well so that no net change in calcium oxalate supersaturation occurred.

## **Consensus**

The citrate literature reviewed here has led to clinical guidelines issued by several relevant associations. The Agency for Healthcare Research and Quality (AHRQ) published a systematic review on the topic of kidney stone prevention. Included in “Key Findings” was: “We found moderate strength of evidence that citrate pharmacotherapy significantly reduces risk of composite recurrent calcium stones”.<sup>121</sup> In addition, the AHRQ review noted that “Further results indicated no significant difference in efficacy between different citrate agents (i.e., potassium citrate, potassium-magnesium citrate, or potassium-sodium citrate)”. The review found that 24.5% of participants randomized to citrate had adverse events versus none

assigned to placebo or control. Specifically, gastrointestinal complaints were reported in 26.2% of participants randomized to citrate versus 16.1% of those assigned placebo or control.

Largely based on the AHRQ review, The American College of Physicians guidelines on kidney stones came to similar conclusions.<sup>122</sup> The guidelines stated that “moderate-quality evidence was derived from 6 trials comparing citrate monotherapy with placebo<sup>123,124</sup> or control<sup>22,37,105,125</sup> in patients with nephrolithiasis.” They stated that pooled data from these trials showed “that composite stone recurrence was lower in patients treated with citrate than placebo or control (11.1% vs. 52.3%).”

Similarly, the guidelines proffered by the American Urological Association are in agreement.<sup>4</sup> The relevant guidelines are three in number. Numbers 15 and 17 were said to reflect moderate evidence, grade B, while number 18 constituted “expert opinion:”

**15. Clinicians should offer potassium citrate therapy to patients with recurrent calcium stones and low or relatively low urinary citrate.**

**17. Clinicians should offer thiazide diuretics and/or potassium citrate to patients with recurrent calcium stones in whom other metabolic abnormalities are absent or have been appropriately addressed and stone formation persists.**

**18. Clinicians should offer potassium citrate to patients with uric acid and cystine stones to raise urinary pH to an optimal level.**

The European Association of Urology guidelines on Urolithiasis were updated in 2020.<sup>126</sup> Among the recommendations in the section on calcium stones is: “Prescribe alkaline citrates and sodium bicarbonate in case of hypocitraturia.” The strength of this guideline is graded as “strong”.

Finally, an authoritative source of systematic reviews is the Cochrane Database for Systematic Reviews, which reviewed the topic of kidney stone prevention in 2015.<sup>127</sup> With access to the same studies reviewed here, and by the AUA and the EAU, the review concludes that “Citrate salts prevent new stone formation and reduce further stone growth in patients with residual stones that predominantly contain oxalate.” Since the number of appropriately conducted trials is relatively low, the evidence was graded “moderate to poor”.

## **Conclusion**

Prevention of kidney stones is considered an important goal of therapy because they are highly recurrent and they incur a cost, both in dollars and in lost quality of life. Prevention can be accomplished by increasing fluid intake, modifying diet and using pharmacologic therapy. Supplementation with alkali citrate remains one of the preferred prophylactic therapy as the evidence in their favor is quite good, they are generally well-tolerated and, until recent years, they were relatively inexpensive. Citrate supplementation can be recommended as an intervention based either on an empiric basis or on a selected basis. The latter requires further metabolic testing, consisting of a 24-hour urine collection, which is done infrequently today. Since citrate is effective in preventing stones regardless of whether patients have hypocitraturia or not, the recommendation to use citrate can proceed empirically, meaning with any calcium stone former in the absence of 24-hour urine data. Randomized controlled trials of alkali citrate for prevention of uric acid and cystine stones are not necessary and will not be done. For those stone compositions, the biochemical and clinical data demonstrating efficacy of urinary alkalization for stone prevention are quite clear and well accepted.

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