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Review Article

# Potassium Citrate: Treatment and Prevention of Recurrent Calcium Nephrolithiasis

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**Abstract**

Nephrolithiasis is a common problem encountered in clinical practice. Almost 2 million outpatient visits for a primary diagnosis of nephrolithiasis were recorded in the year 2000 in the United States [1]. This condition affects approximately 5-10% of adults during their lifetime and may also affect the pediatric population. Recurrence is present in almost 50% of patients within 5 years of their initial stone event. Despite successful therapy, stone-free rate will be approximately of 75% at 18 months [2]. After diagnosis of nephrolithiasis, subsequent therapy must be considered based upon the type of stone and the biochemical abnormalities that are present. Approximately 75% of patients with nephrolithiasis form calcium stones, most of which are composed primarily of calcium oxalate [3]. Medical therapy is usually undertaken in patients that have had recurrent calcium stones. The administration of potassium citrate, an oral alkalizing agent, acts as a potent inhibitor of calcium stone formation and has been used as the mainstay of medical nephrolithiasis management in the last 3 decades.

This review provides an overview of the use of potassium citrate in the clinical management of calcium nephrolithiasis. Mechanism of action, benefits and possible risks of potassium citrate intake will be reviewed.

## ABBREVIATIONS

ACE: Angiotensin-Converting-Enzyme inhibitor; RTA: Renal Tubular Acidosis; GI: Gastrointestinal

## INTRODUCTION

Urinary stone disease is common and poses a significant health care burden in a working-age population. In 1994, data from the National Health and Nutrition Examination Survey (NHANES) estimated the prevalence of stone disease at 6.3% among men and 4.1% among women [4]. The prevalence and incidence of nephrolithiasis in the United States is increasing and is markedly higher than when last measured in 1988–1994 [5]. A more recent study found that among men, the prevalence of stones was 10.6%, compared with 7.1% among women [5]. The cause of this increase is most likely due to factors related to dietary and life style changes [5-7]. The lifetime prevalence of nephrolithiasis in adults ranges between 3.4-10.6% for men and 3.4-7.1% for women, progressively increasing with age [5]. History of stone disease has also been associated with socioeconomic status. Individuals with an annual household income ≤$19 999 were more likely than individuals earning >$75 000 annually to report a history of kidney stones. Furthermore, individuals with an annual household income between $20 000 and $34 999 showed a similar increase in risk compared with the high-income group [5]. The annual medical expenditures for management of nephrolithiasis were estimated at $2.1 billion in 2000 representing a 50% increase since 1994 [8,9].

Cost-benefit of medical therapy for prevention of urinary stone recurrence has been an interrogation for clinical practitioners [8-13]. Medical therapy for prevention of stone recurrence may be more effective than conservative measures, even though this may represent higher costs [10,14-17]. A treatable metabolic etiology of stone formation can be detected in more than 95 percent of patients evaluated for stone disease. Directed medical therapy based on metabolic evaluation is often instituted in patients with high risk of stone recurrence [10]. This group of patients includes those with a strong family history of stones, gastrointestinal disorders such as chronic diarrhea, gout, bone disease, urinary tract abnormalities, and children with nephrolithiasis and patients with a solitary kidney or severe medical comorbidities. Soygur and colleagues, while studying the efficacy of potassium citrate treatment in preventing stone recurrences was evaluated, they found that the medically treated patients had a significantly greater remission rate than the untreated patients (44.5 v 12.5%; $P < 0.05$) [18]. Approximately 75% of patients with nephrolithiasis form calcium stones, most of which are composed primarily of calcium oxalate or, less often, calcium phosphate which accounts for 20-40% of stones

analyzed [3,5]. Patients with calcium-based stones may have multiple metabolic abnormalities related to their diagnosis, including hypercalciuria, hypocitraturia, hyperoxaluria, gouty diathesis, hypomagnesuria and low urine volumes.

## MECHANISM OF ACTION OF POTASSIUM CITRATE

Citrate is a weak acid that is synthesized inside Krebs' cycle. It can also enter the body through dietary intake [19]. In the clinical setting, potassium citrate has been used as an oral alkalinizing agent, and it has remained the mainstay of medical treatment for nephrolithiasis during the last 3 decades. The gastrointestinal tract will absorb nearly all of this supplementary citrate. This citrate load is then delivered to the liver where it is metabolized to bicarbonate, therefore producing an alkaline load. The residual load of citrate that is not metabolized by the liver moves into the serum to later be excreted by the kidneys. Citrate levels relate directly with urinary pH levels. When urinary pH rises, renal citrate production does as well, thus producing decrease in tubular citrate reabsorption [20,21]. The net effect is decreased citrate uptake and increased citrate excretion. In addition to the effect on pH, some of the administered citrate may be excreted directly before being metabolized to bicarbonate [22]. Therefore, potassium citrate has a slightly higher citraturic impact on urinary citrate than potassium bicarbonate [22,23]. Differences in intestinal handling, serum concentration as well as filtered load of citrate are not found between kidney stone formers and normal subjects. On the contrary, several metabolic abnormalities, such as metabolic acidosis, hypokalemia and starving, seem to influence the renal handling of citrate by inducing a decrease in the urinary citrate excretion [19]. Crystallization of stone forming salts such as calcium oxalate, calcium phosphate and uric acid, is inhibited by potassium citrate [24,25]. The changes obtained lead to decreased saturation of calcium oxalate. Urinary saturation of calcium phosphate, however, may not be altered by potassium citrate, given that the effect of increased citrate complexation of calcium is opposed by the rise in pH-dependent dissociation of phosphate. In summary, the net effect of potassium citrate is decreased citrate uptake and increased citrate excretion. In addition to the effect on pH, some of the administered citrate may be excreted directly before being metabolized to bicarbonate. [22] Therefore, it decreases urinary calcium and calcium oxalate saturation, increases urinary uric acid concentration but also increases urinary uric acid solubility and has nearly no change on urinary oxalate or sulfate.

## INDICATIONS FOR POTASSIUM CITRATE

According to AUA guidelines, clinicians should offer potassium citrate therapy to patients with recurrent calcium stones and low or relatively low urinary citrate [26]. Patients with the following conditions are included:

1. Hypo citraturic nephrolithiasis of any etiology
2. Hyper calcuric patients in conjunction with thiazides
3. Renal tubular acidosis (RTA)
4. Chronic diarrheal syndromes
5. Gouty diathesis associated with uric acid stones or calcium oxalate stones

## POTASSIUM CITRATE IN HYPOCITRATURIA

Hypocitraturia or low urinary citrate excretion is a common feature in patients with nephrolithiasis, particularly in those with calcium stone disease [19]. It is a metabolic abnormality that can be detected at up to 10% in isolation and up to 63% or in combination with other urinary disorders among patients with nephrolithiasis [27]. Normal range of urinary citrate may vary among laboratories. Urine from normal women contains an average of 59.5 mg of citrate per deciliter (3.10 mmol per liter) and 10.5 mg of calcium per deciliter (2.62 mmol per liter), as compared with 43.2 and 15.7 mg per deciliter (2.25 and 3.92 mmol per liter), respectively, in normal men [3]. Multiple risk factors have been known to cause hypocitraturia, therefore contributing to stone formation. These risk factors include chronic diarrhea, distal renal tubular acidosis (RTA), metabolic acidosis, and medullary sponge kidney. Furthermore, a few pharmacological therapies that include the use of anhydrase inhibitors; ACE inhibitors; topiramate and lithium have also been reported to cause hypocitraturia [21]. Increasing urinary citrate excretion is the goal in patients with hypocitraturia since citrate inhibits stone formation by forming a poorly dissociable but soluble complex with calcium, thus reducing the amount of calcium available for binding with oxalate or phosphate [23]. Medical therapy with oral alkalinizing salts such as potassium citrate continues to be the treatment of choice in patients with hypo citraturic nephrolithiasis, inasmuch as for its citrate content as well as the alkali load delivery to the kidneys. Therefore, citrate excretion can be enhanced by alkalinizing the plasma by the daily administration of 30 to 80 meq of potassium citrate or potassium bicarbonate [23]. There are a variety of citrate supplements available; however potassium citrate remains the option of choice over sodium citrate. Since the 1980s, it is the most commonly prescribed citrate preparation [25, 28-30]. In a meta-analysis where four trial studies of citrate therapy compared with placebo or no treatment were compared, citrate significantly reduced the incidence of stone recurrence (relative risk 0.25, 95% CI 0.14-0.44) [31].

## CHRONIC DIARRHEA

Citrate is the main substance in the body responsible for inhibiting calcium stone formation [32]. In stone formers, hypocitraturia can occur alone or in combination with other metabolic abnormalities such as high urine calcium or high urine oxalate. Although variably defined, hypocitraturia is considered as citrate excretion of less than 320 mg/day [32]. Metabolic acidosis induced by chronic diarrhea leads to renal citrate reabsorption, therefore reducing urinary excretion [26]. In cases of chronic diarrhea, the powder (liquid) form is the best choice. For adults with idiopathic hypocitraturia, and normal renal function, a dose of 40 to 60 mEq of potassium citrate per day is suggested [20]. In the case of hyperoxaluria, a low oxalate diet is recommended. Other treatment measures include [33] increasing fluid intake, calcium supplements or vitamin B6 to control this condition [34].

## RENAL TUBULAR ACIDOSIS (RTA)

RTA is known to be associated with hypo citratura, alkaline urine, acidosis and hypokalemia. Patients with RTA and nephrolithiasis should undergo a metabolic evaluation to design

the optimal regimen to prevent growth of existing stones and new stone formation. Urinary pH > 6.5, hypo kalemic acidosis and nephrocalcinosis, in young female patients who present with profound hypocitraturia, often present with RTA as well.

## THIAZIDE-INDUCED HYPOCITRATURIA

Thiazide therapy often leads to hypokalemia and hypocitraturia. The intracellular acidosis caused by hypokalemia will enhance citrate metabolism, thereby lowering the cell citrate concentration and creating a more favorable gradient for citrate reabsorption [22,35]. Potassium citrate is therefore commonly administered in conjunction with thiazides used for the treatment of hypercalciuria [36,37].

Patients with high urine calcium that is not due to hypercalcemia and persistent active stone disease should be treated with normal calcium, reduced animal protein, and low salt diet, plus a thiazide diuretic such as hydrochlorothiazide or chlorthalidone [38]. Thiazide therapy can lower calcium excretion by as much as 50 percent. This is primarily by inducing mild volume depletion, leading to a compensatory rise in the proximal reabsorption of sodium, and therefore of passive calcium reabsorption [39,40]. In a meta-analysis of five trials of thiazide diuretics compared to standard treatment, thiazide therapy was associated with a significant reduction in the number of new stone recurrences (relative risk 0.52, 95% CI 0.39-0.69) [31].

## GOUTY DIATHESIS ASSOCIATED WITH URIC ACID STONES OR CALCIUM OXALATE STONES

Patients with gouty diathesis are often treated with potassium citrate (low urinary PH < 5.5), whether it is an isolated metabolic abnormality or it's associated with other abnormalities. There are no randomized trials that have evaluated the efficacy of urinary alkalization on recurrence or dissolution of uric acid stones. However, alkalization is associated with a remarkable reduction in recurrent stone episodes in observational studies.

Alkalization therapy should target a urine pH between 6 and 6.5. Allowing urine pH to rise higher than 7 will not provide significant benefit to uric acid stone formation and may increase the risk of calcium phosphate stone formation. An alkaline urine pH may not need to be maintained at all times since raising the urine pH to at least 6.5 once per day or every other day prevents uric acid stone formation [41].

## EFFECTIVENESS OF LONG-TERM POTASSIUM CITRATE THERAPY

Potassium citrate therapy is effective and safe, proven by its use as medical prophylaxis in stone formers for the last three decades. In a retrospective study, 503 patients who received potassium citrate for a mean duration of 41 months (range 6-168) were evaluated. Urinary profile changes such as increased urinary pH (5.90 to 6.46, $p < 0.0001$) and increased urinary citrate (470 to 700 mg a day, $p < 0.0001$) were recorded at 6 months after the onset of therapy. There was a significant decrease in stone formation rate after the initiation of potassium citrate from 1.89 to 0.46 stones per year ($p < 0.0001$). A 68% remission rate and a 93% decrease in stone formation rate were observed. Changes in urinary metabolic profiles were sustained for as long as 14 years of treatment. The results obtained by this study confirmed the long-term effectiveness of potassium citrate therapy in patients with recurrent nephrolithiasis [16]. It is essential that all the relevant urinary factors be monitored in individuals with calcium oxalate stones as they often have more than one urinary abnormality.

## IMPACT OF POTASSIUM CITRATE ON RESIDUAL STONES AFTER SURGICAL TREATMENT

Pharmacological therapy after surgical management of nephrolithiasis such as percutaneous nephrolithotomy and shock wave lithotripsy has, in multiple studies, demonstrated to have a beneficial effect. This may help correction of metabolic abnormalities, prevention of stone recurrence and decrease the frequency of future surgical procedures for stone removal. The beneficial effects of medical therapy were observed in patients with or without residual stone fragments after surgical management or shock wave lithotripsy [15,17,18,42-45].

## DOSE ADJUSTMENTS AND FOLLOW-UP

Pharmacological therapy for calcium based stones in hypocitraturia, aims to maintain urinary pH between 6 and 6.5 in stone formers with low urinary pH. Depending on the severity of hypocitraturia, the initiating dose ranges between 30 and 60 mEq, 2-3 times a day and is usually ingested with meals. The dose must be adjusted in patients with renal insufficiency, as it may represent further renal damage. Therapy with potassium citrate must begin gradually to obtain better tolerability and in this manner avoid side effects. Monitoring of serum electrolytes and creatinine is done before and 2-3 weeks after therapy, especially patients at higher risk of electrolyte disorder. If hyperkalemia or serum creatinine rises, treatment must be discontinued. Dose adjustment is done according to urinary pH and changes in metabolic profile, therefore metabolic profiles based on 24-hour urine collections should be done initially around 4 months after initiating treatment. Follow up intervals should increase gradually to 6 and later to 12 months.

## ADVERSE REACTIONS AND COMPLIANCE

One of the major challenges to obtain successful outcome of medical therapy for prevention of stone growth/recurrence is patient compliance. Due to this, dietary modification is in occasions presented to patients as the first alternative of treatment. In a Swedish center, a survey was performed in 100 patients undergoing intervention for nephrolithiasis, 95% patients were motivated to change their dietary habits, whereas only 71% desired pharmacologic treatment. Collection of 24-h urine for risk evaluation in one or five fractions was acceptable to 94% of men and 84% of women [46]. A few of the reasons for poor compliance reported, have been related to high cost, gastrointestinal side effects (abdominal pain, nausea, vomiting, diarrhea), bad taste, and inconvenience of bid or tid dosing [27,47,48]. Additional to this, gastrointestinal side effects were reported in 10% of patients on potassium citrate therapy [21,28,49]. Tablet presentation of potassium citrate is commonly used, however powder/liquid form is recommended in patients with associated chronic diarrhea. Poor compliance to the powder form of potassium citrate may be seen in patients with poor

palatability, adding artificial sweetener could avoid this. A recent study was done where comparison between Splenda + potassium citrate compared with potassium citrate alone was evaluated. Beneficial effects were compared to baseline, and though 24-hour citrate, K, and pH were significantly higher compared to baseline, no significant difference from each other was observed. The study concluded that Splenda significantly improved the palatability of potassium citrate therapy and did not alter the beneficial effects of potassium citrate on 24-hour urine citrate, K, or pH [48].

## CONTRAINDICATIONS AND PRECAUTIONS

Though potassium citrate therapy has proven to be effective in the management and recurrence of stone disease, possible side effects have been reported. The use of potassium citrate should be with held from patients with hyperkalemia from any cause, due to the risk of producing cardiac arrest. Furthermore, severe renal insufficiency, oliguria, or azotemia; potassium-restricted diet; untreated Addison's disease; acute dehydration; heat cramps; anuria and severe myocardial damage are common contraindications to the use of potassium citrate. Additionally, Potassium citrate should not be used when GFR is reduced (creatinine > 2.5 mg/dl). Potassium citrate may cause irritation to the GI tract, such as nausea, vomiting, diarrhea, abdominal pain and discomfort that could further lead to GI ulceration, bleeding, perforation and/or obstruction. In any of these cases, potassium citrate must be immediately discontinued. Finally, alternatives to potassium citrate should be considered by clinicians when treating patients in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract, such as those suffering from delayed gastric emptying, esophageal compression, intestinal obstruction or stricture, or those taking anticholinergic medication.

## DIETARY ALTERNATIVES AND ADJUNCTS TO POTASSIUM CITRATE THERAPY

Potassium citrate therapy, though it has demonstrated to be the best option for management and recurrence of calcium nephrolithiasis in hypocitraturic stone formers, there are patients who would rather receive non-pharmacological intervention. Several studies have investigated the impact of citrus juices on urinary profiles of patients with nephrolithiasis [21,50-55]. Orange juice can increase urinary pH and citrate [54].

The impact of orange, grapefruit or apple juice on urinary profiles has also been investigated. Citrate excretion and pH increase was observed in all three juices, however, decrease in relative supersaturation of calcium oxalate crystallization was only significant for grapefruit juice [54]. In another study, an increase was found in urinary oxalate and citrate excretion with no change in the supersaturation of calcium oxalate, calcium phosphate, or uric acid [55].

Of all citrus juices studied, lemon juice has shown to have the highest concentration of citrus. Lemon juice produces an increase in urine volume and citrate, and a decrease in urinary calcium. It is a well tolerated source of citrate that has proven to be inexpensive, as shown by previous studies, hence improving patient compliance and the chance to be used as adjunctive therapy in patients with hypocitraturia [10,50-52,56]. A risk that has been seen with orange juice administration is the increase of urinary oxalate; this was not observed in patients who were treated with lemonade therapy [51]. Long-term lemonade therapy was able to decrease the stone formation rate from 1.00 to 0.13 stones per patient per year ($p < 0.05$) [51]. Though most patients prefer dietary changes, it should be taken into consideration that slow release potassium citrate therapy has a significantly greater citraturic response compared to lemonade therapy. The citraturic action of potassium citrate may be attributed to the effect of alkali load delivered by oxidation of citrate to bicarbonate combined with the direct renal excretion of citrate [16,20,21,25,51,57]. On the other hand, lemonade therapy is not able to deliver a urinary alkali load due to the low pH of lemon juice.

## CONCLUSIONS

Recurrent stone formers may need a multi-modal approach of medical therapy, life style changes, dietary adjustments to control multiple or complex metabolic abnormalities. Potassium citrate therapy directed by metabolic evaluation is an effective and safe medical therapy for recurrent stone formers; with appropriate follow up.

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