

Therapy of nephrolithiasis: where is the evidence from clinical trials?

Tratamento da nefrolitíase: onde está a evidência dos ensaios clínicos?

Authors

Maria Aparecida Pachaly¹
Cristina Pellegrino Baena²
Maurício de Carvalho^{1,2}

¹ Universidade Federal do Paraná.

² Pontifícia Universidade Católica do Paraná.

ABSTRACT

The prevalence of kidney stone disease is increasing worldwide with significant health and economic burden. Newer research is finding that stones are associated with several serious morbidities. Yet, few randomized clinical trials or high quality observational studies have assessed whether clinical interventions decrease the recurrence of kidney stones. Therefore, in this review we analyze the available evidence on medical expulsive therapy for ureteral stones; describe the evidence about non-pharmacological stone therapy including dietary modifications and citrus juice-based therapy; and discuss the efficacy of thiazide diuretics for the treatment of hypercalciuria in recurrent nephrolithiasis.

Keywords: citric acid; hypercalciuria; kidney calculi; nephrolithiasis; potassium citrate.

RESUMO

A prevalência da nefrolitíase está aumentando em todo o mundo e resulta em ônus significativo para o sistema de saúde. Novos estudos revelam que a formação de cálculos urinários está associada a várias morbidades graves. No entanto, poucos estudos observacionais ou ensaios clínicos randomizados de qualidade demonstraram que intervenções clínicas específicas diminuem a recorrência da nefrolitíase. Portanto, nesta revisão são analisadas as evidências disponíveis da terapia médica expulsiva para cálculos ureterais; avaliam-se os dados da terapêutica não farmacológica, incluindo modificações dietéticas e terapia à base de sucos cítricos; e discute-se a eficácia dos diuréticos tiazídicos no tratamento da hipercalciúria associada à nefrolitíase recorrente.

Palavras-chave: citrato de potássio; cálculos renais; hipercalciúria; nefrolitíase; ácido cítrico.

INTRODUCTION

The occurrence of urolithiasis is high and increasing worldwide. The lifetime risk of symptomatic kidney stones is approximately 13% in men and 7% in women.¹ In addition, its recurrence rate is also elevated. Once diagnosed, 50% of adult urolithiasis patients recurred in 5-10 years and 75% in 20 years.²

Most patients with nephrolithiasis present symptomatically, usually with flank or abdominal pain. Other potential manifestations include gross hematuria, dysuria, nausea/vomiting, and spontaneous elimination. Approximately one third of the patients are asymptomatic, primarily diagnosed when abdominal imaging is performed for other purposes.³

Analysis of risk factors for nephrolithiasis by 24-hour urine is essential to prevent kidney stone recurrence. Hypercalciuria, the most common metabolic abnormality found in calcium stone formers, even being often familial and idiopathic, is mainly influenced by diet.⁴ Hypercalciuria increases urine supersaturation and promotes crystal formation and growth. Urinary citrate also plays an important role in reducing the formation and recurrence of kidney stones by chelating calcium, inhibiting spontaneous nucleation and aggregation of oxalate crystals and interacting with Tamm-Horsfall protein to inhibit calcium oxalate crystallization.^{5,6}

The current therapies for prevention of recurrent kidney stones all are relatively ancient and only a handful of drugs

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Correspondence to:

Maurício de Carvalho.
Universidade Federal do Paraná and
Pontifícia Universidade Católica do
Paraná.
Rua General Carneiro, nº 181, Curitiba, PR, Brazil. CEP: 80060-900.
E-mail: carvalho@mais.sul.com.br

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are commonly used today, none of which is less than 30 years old.⁷ In contrast, there are several new options to medical expulsive therapy (MET) described as a conservative treatment option in the initial management of small ureteral stones. This brief narrative review intends to: 1) present the available evidence on the MET; 2) describe some evidence about non-pharmacological stone therapy including dietary modifications and lemonade or other citrus juice-based therapy, and 3) discuss the effects of thiazide diuretics for the treatment of hypercalciuria in recurrent nephrolithiasis. Because of space limitations, this review is not intended to be exhaustive, but try to provide an evidence-based, patient-oriented analysis on the topic. Prospective randomized controlled trials and meta-analysis will be emphasized, whereas uncontrolled and retrospective studies will be mentioned.

MEDICAL EXPULSIVE THERAPY (MET)

The two most important factors in predicting the ureteral stone passage are stone size and location.⁴ Distal ureteral stones 5mm or smaller in size have about a 50-70% probability of passing spontaneously. Stones between 5-10 mm have less than 50% of chance.⁸ Calcium-channel blockers and α -1 blockers have emerged as the most promising agents for MET. Calcium-channel blockers (such as nifedipine) suppress smooth muscle contraction and reduce ureteral spasm, whereas α -1D adrenergic receptor antagonists (e.g. tamsulosin) decrease ureteral smooth muscle tone, frequency, and force of peristalsis.⁹

Several randomized but unmasked trials have been conducted on small cohorts of patients. In 2006, a large meta-analysis by Hollingsworth *et al.*¹⁰ studied 693 patients with ureteral stones (mean stone size, 3.9 to 7.8 mm) randomized to receive calcium-channel blockers, α -1 blockers, or no therapy for 1 to 6 weeks, and followed for 15 to 48 days. In three trials, patients received corticosteroids in addition to nifedipine, and in seven trials, both treated and control groups received nonsteroidal anti-inflammatory drugs. Patients treated with alpha-blockers had a 65% greater likelihood of spontaneous stone passage and a pooled risk ratio of 1.54 (confidence interval [CI] 1.29-1.85) when compared to control ($p < 0.0001$). The most common side effect reported was transient hypotension at 3.3% to 4.2%.¹⁰ However, the authors emphasized that their results were probably limited by

a publication bias, which may have led to an overestimation of treatment effect and clearly advocated for a large, well-performed randomized clinical trial (Table 1).

A large, well powered, placebo-controlled, multicenter, randomized trial was just published.¹¹ In the Spontaneous Urinary Stone Passage Enabled by Drugs (SUSPEND) trial, conducted in National Health Service hospitals in the United Kingdom, 1,136 patients harboring a single ureteral stone < 10 mm (located at any site in the ureter) were randomized to a 4-week trial of tamsulosin, nifedipine, or placebo. The primary outcome was spontaneous stone passage in 4 weeks, defined as the absence of need for additional interventions to effect stone passage.¹¹ During treatment, about 80% of patients in each group did not require additional interventions to assist with stone passage. A similar percentage of tamsulosin-, nifedipine-, and placebo-group participants had interventions planned at 12 weeks (7%, 6%, and 8%). There was a trend toward significance for MET, specifically with tamsulosin in women with calculi >5 mm, and for calculi located in the lower ureter. Secondary outcomes, such as pain and time to stone passage, were not significantly different among the groups. Two limitations of the trial: high percentage of patients not adhering to the medications and the use of a questionnaire instead of radiographic or endoscopic proofs of stone expulsion (Table 2).

Very recently, Furyk *et al.*¹² assessed the efficacy and safety of tamsulosin compared with placebo as MET in patients with distal ureteric stones less than or equal to 10 mm in diameter. It was a multicenter, randomized, double-blind, placebo controlled trial conducted in 5 emergency departments (EDs) in a single state in Australia. In 316 patients with symptomatic stones and 28-day computed tomography follow-up, the rate of stone passage (primary outcome) was similar between tamsulosin and placebo. However, in a subgroup analysis (although pre-specified by the investigators) 103 patients with 5- to 10-mm stones had their stone passed more frequently with tamsulosin. This trial possesses several limitations. They found poor compliance to the treatment regimen under trial conditions. In addition, the possibility of some selection bias cannot be excluded because recruitment was done by busy staff of an ED with competing priorities (Table 2).¹²

TABLE 1 MEDICAL THERAPY TO FACILITATE URINARY STONE PASSAGE

TITLE	Exposure	Outcomes	Conclusion
Medical therapy to facilitate urinary stone passage: a meta-analysis ¹⁰	The authors identified and summarized all randomized controlled trials in which calcium-channel blockers or α blockers was used. Only 9 (n = 693) of over 400 studies fit the inclusion criteria.	The main outcome was the proportion of patients who passed stones ≤ 6 or ≥ 6 mm	Findings suggest that MET is an option for facilitation of urinary-stone passage (ARR = 0.31, 95% CI-0.25-0.38). High-quality, randomized trial is necessary to confirm its efficacy
META-ANALYSIS REVIEW CRITERIA			
Question	Answer	Question	Answer
1. Was the clinical question sensible and answerable?	Yes	6. Were the outcomes clinically relevant?	Yes
2. Were studies selected and data extracted by 2 or more individuals?	Yes	7. Was there low statistical heterogeneity for the primary outcome?	Yes, 28%; not significant
3. Was the search for studies detailed and exhaustive?	No, the authors did not state how the papers were selected for the review	8. Was the treatment effect large enough and precise enough to be clinically significant?	Yes
4. Were primary studies of high methodological quality?	No, eight of which were not blinded and six of which did not describe the randomization procedures	9. Was there any conflict of interest?	No
5. Were the assessments of studies reproducible?	Yes	10. General comments	Sample sizes were small and methodologies varied

TABLE 2 MEDICAL EXPULSIVE THERAPY IN ADULTS WITH URETERIC COLIC: RANDOMIZED CLINICAL TRIALS

Title	Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial ¹¹	Distal Ureteric Stones and Tamsulosin: a Double-Blind, Placebo-Controlled, Randomized, Multicenter Trial ¹²
Exposures	Tamsulosin 0.4 mg, nifedipine 30 mg, or placebo; expectant management for a single ureteral stone identified by CT at 24 UK hospitals	0.4 mg of tamsulosin or placebo daily for 28 days identified by CT at 5 EDs in Australia
Outcomes	Proportion of participants who did not need further intervention for stone within 4 weeks of randomization	Stone expulsion on CT at 28 days and time to stone expulsion
Conclusion	Tamsulosin 0.4 mg and nifedipine 30 mg are not effective	The rate of stone passage (primary outcome) was similar between tamsulosin and placebo. In the subgroup with 5- to 10-mm stones, tamsulosin increased clearance.
Randomization	Yes	Yes
Allocation concealment	Yes	No
Blinding participants	Yes	Yes
Blinding outcome assessor	Yes	Yes
Loss-to-FUP	Not important to the results	17%; Sensitivity analysis were conducted and they didn't change the results materially
Selective reporting	No	No
Intention-to-treat	Yes	Yes
Other bias	No	No

NON-PHARMACOLOGICAL STONE THERAPY

The typical diet in industrialized countries, high in sodium, animal proteins and beverages sweetened with sugar and fructose results in high excretion of calcium, uric acid, oxalate and phosphorus and a decrease of urinary citrate and pH, thus favoring formation of kidney stones.^{13,14}

Diet may promote or inhibit the formation of calcium oxalate urinary stones. General dietary recommendations play a central role in preventing nephrolithiasis, and nowadays rely mainly on maintaining a normal calcium content, increasing intake of fluids, fruits and vegetables, and reducing sodium and animal protein.¹⁵ Preventive dietary recommendations should be adapted to the results of stone composition or urinary risk factors.

FLUIDS

One of the simplest and most important recommendations for the prevention of nephrolithiasis is the ingestion of fluids in sufficient amounts to produce a daily urine volume of more than 2 liters/day.¹⁵ A low volume of urine is a major risk factor for nephrolithiasis, and is present without other serum or urine predisposing factor in a considerable proportion of stone formers.¹⁶

The intake of over 2.5 liters of fluids per day, being at least 50% water, is associated with a decrease in the relative risk of urinary stones.^{17,18} With increased intake of mineral water, there is some concern about the amount of electrolytes ingested. There is a wide variation in the mineral content of commercially available mineral water, and this fact must be taken into account. However, the clinical impact of water hardness (combined calcium and magnesium concentrations) in nephrolithiasis remains uncertain, since most studies have shown poor correlation between the hardness index and the urinary excretion of calcium, magnesium and citrate.¹⁸

Dietary modifications that include citrate-rich fluids can be an option to pharmacological agents. We recently published a systematic review and meta-analysis on the effects of non-pharmacological interventions on urinary citrate and nephrolithiasis.¹⁹ Thirteen studies with 358 participants (mean age 43 ± 11.0 years) were included. Interventions were: commercial fruit juices, soft drinks, calcium/magnesium-rich mineral water, high-fiber diet, low-animal-protein diet and a plant extract. Almost half

of the studies reported effects in non-stone formers. Commercial fruit juice interventions caused an increase in citraturia levels of 167.2 mg/24 h (95% CI 65.4 to 269), but with a high heterogeneity index (I^2 88,1%, $p = 0.000$). Other types of intervention had small number of samples and did not show important heterogeneity. However, pooled estimates were not significant. Our review suggests the need for methodological improvement on this area. Available evidence indicates that larger scale trials are needed to conclude whether non-pharmacological interventions can increase urinary citrate levels and act in kidney stone prevention.¹⁹

FRUCTOSE AND SUCROSE

The increasing use of sucrose and refined fructose in recent decades, especially in soft drinks and other foods, relates to lithogenesis through the induction of obesity and also through the kidney effects of fructose, causing insulin resistance, decreased urinary pH, and increased urinary excretion of calcium, oxalate and uric acid.²⁰ Fruits contain varying amounts of fructose, but the fructose therein is bound to fibers and other substances that reduce its absorption (unlike what occurs with industrialized-occurring fructose).

PHARMACOLOGIC THERAPY OF HYPERCALCIURIA WITH THIAZIDES

Thiazides have been demonstrated to decrease hypercalciuria by causing sodium depletion (albeit modest), which is associated with a fall in urine calcium excretion; this effect can be prevented by administration of sodium chloride.²¹ In addition, there might be a component of direct enhancement of calcium absorption in the distal nephron, due to upregulation of distal tubule calcium channel (TRPV5) and increases in calbindin expression.²²

Several studies have demonstrated the beneficial effects of thiazides in preventing kidney stone recurrence. There are at least 10 RCTs and seven of them reported a reduction in recurrence rate in treated patients.²³ Although most patients in these trials made calcium oxalate stones, several patients formed stones composed by calcium phosphate. From these trials, only four studies (295 adult patients) reported data of stone-formers with documented hypercalciuria.²⁴⁻²⁷ Escribano *et al.*,²⁸ in a Cochrane review analyzing pharmacological interventions in idiopathic hypercalciuria, found a significant decrease in the

number of new stone recurrences in those treated with thiazides (RR 1.61, 95% CI 1.33 to 1.96). The stone formation rate also showed a statistically significant decrease (MD -0.18, 95% CI -0.30 to -0.06). The follow-up periods of these studies varied from 5 months to 3 years. Table 3 summarizes the main characteristics of included studies. Recent guidelines recommends pharmacologic monotherapy with a thiazide diuretic to prevent recurrent nephrolithiasis in patients with active disease in which increased fluid intake fails to reduce the formation of stones (Grade: weak recommendation, moderate quality evidence).^{29,30}

When we critically analyze these trials, significant questions were left unanswered. As showed in Table 3, much of our current recommendations for managing hypercalciuria with thiazides are based on works from the 80-90s. Maybe for these reason most of them do not report measurements of vitamin D and its metabolites. This is relevant since epidemiologic studies have reported associations between urinary calcium excretion and serum levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D.³¹ In addition, in these studies follow-up or diagnosis of the stones was not made by new,

TABLE 3 RANDOMIZED CLINICAL TRIALS OF THIAZIDE TREATMENT IN HYPERCALCIURIC STONE FORMERS

Abridged title	Unprocessed bran and intermittent thiazide in prevention of recurrent stones ¹⁶	Thiazide for calcium urolithiasis in patients with hypercalciuria ¹⁷	Randomized prospective study of indapamide in preventing calcium stone recurrences ¹⁸	The role of thiazides in the prophylaxis of recurrent calcium lithiasis ¹⁹
Year	1987	1992	1993	2006
Exposures	Group A: n: 18; Bran (40 g/d). Group B n: 14; Bran (40 g/d) + thiazide (50 mg twice a day)	Group A: n: 93 No specific therapy Group B: 82 Trichlormethiazide (4 mg/d)	Group A: n:25; diet and fluid. Group B: n:25; diet and fluid + indapamide (2.5 mg/d). Group C: n:25; diet and fluid + indapamide (2.5 mg/d) + allopurinol (300 mg/d)	Group A: n: 17; no specific therapy Group B: n: 21; hydrochlorothiazide (50 mg/d) Group C: n: 14; Hydrochlorothiazide (50 mg/d) + potassium citrate (20 mL Eq/d)
Outcomes	Stone/year per patient; stone-free patients (%) mean urinary excretion of lithogenic factors	Stone formation rate (stones/patient/y) Stone-free patients (%) Reduction in stone formation Remission rate Total number of newly formed stones	Stone formation rate (stones/patient/y); stone-free patients (%); reduction in calciuria and oxaluria	Stone-free patients (%)
Conclusion	Thiazide + bran superior. 3/11 (27%) stones compared with the 11/17 (65%) in the bran group.	Stones/patient/year lower in the thiazide group (0.13 versus 0.31), with statistically significant difference.	Urinary calcium decreased to 50% of the pretreatment values; stone rate improved more in the two drugs Tx groups	Recurrence of 19% (4 cases) and 7% (1 case) in groups B-C, respectively compared to 59% (10 cases) of group A, p = 0.003
Randomization	Yes; however method not described	Yes; however method not described	Yes; however method not described	Yes; however method not described
Allocation concealment	Unclear	Unclear	Unclear	Unclear
Blinding participants	No	No	No	No
Blinding outcome assessor	No	No	No	No
Loss-to-FUP	Not reported	Yes, 35/175	Yes, 11/75	No
Selective reporting	Unclear	Unclear	Unclear	No
Intention-to-treat	Yes	No	No	No
Other bias	No	No	No	No

more sensitive and specific radiologic methods, as non-enhanced computed tomography (CT) scanning. When available, CT is now considered the examination of choice for the detection and localization of urinary stones.³²

Researchers in these trials employed various thiazide-type agents with different doses. However, maybe due to a practice pattern of using lower doses of hydrochlorothiazide for the treatment of hypertension and/or a lack of knowledge of RCT of thiazide diuretics in nephrolithiasis recurrence, Vigen *et al.* found that only 35% of hydrochlorothiazide-treated patients received 50 mg/day, a dose previously shown to reduce stone recurrence.³³ Hyperglycemia, hyperlipidemia, hyperuricemia, hypokalemia and hypomagnesemia are all metabolic, dose-dependent side effects induced by thiazide diuretics. Therefore, limiting the dose administered to decrease calciuria sounds reasonable. However, a small study with 6 non-stone formers subjects could not show a statistically significant reduction in urinary calcium with 12.5 mg/day of hydrochlorothiazide, 25 mg/day showed some response and doses of 50 mg/day showed the most significant reduction in urinary calcium.³⁴ Additionally, thiazide therapy may induce hypocitraturia owing to hypokalemia with resultant intracellular acidosis.² Therefore, concurrent treatment with potassium citrate should be considered in normocitraturic stone-forming patients who are on a thiazide for hypercalciuria.

As stated before, all the studies presented in Table 3 had a short follow-up. In the average population of recurrent stone-formers, the annual frequency of stone formation is less than 0.15-0.20. For this reason it is difficult to draw conclusions from treatment periods of less than 5-7 years.³⁵ It is also worrisome that some (small) studies documented a limited long-term effectiveness of thiazides. In the so-called absorptive hypercalciuria type I, hydrochlorothiazide was effective in reducing urinary calcium excretion only during the first 2 years of treatment.³⁶ Therefore, the ideal length of treatment of hypercalciuria in nephrolithiasis patients is still unknown.

There is a linear association between salt intake and calcium excretion. A 6 g/day increase in salt intake may result in a 80 mg/day increase in urinary calcium in stone formers *versus* 40 mg/day in non-stone formers.³⁷ Sodium restriction is also essential in patients who require thiazides for the treatment of

hypercalciuria. If dietary sodium is high (> 100mEq/day), the hypocalciuric effect of thiazides can be attenuated.³⁷ Nowadays, high salt ingestion is much more prevalent than two decades ago, potentially blocking the full action of thiazides. In fact, in our experience 45.2% of stone-formers had sodium intake above recommended levels. Yet, sodium intake may have been underestimated, since the salt added by the patients was not considered in our study.³⁸

When compared to some years ago, a large proportion of nephrolithiasis patients today exhibit high BMI (classified as overweight or obesity), increased waist circumference, and high body fat percentage.³⁹ Obesity is associated with metabolic disorders that might favor kidney stone formation, like *diabetes mellitus*, for example. In addition, excess weight might increase the urinary excretion of uric acid and oxalate, which are known risk factors for calcium oxalate stones.³⁹ Several studies stressed the ability of thiazides to exacerbate features of metabolic syndrome and/or increase the risk for developing diabetes. The thiazide-induced hyperuricemia and hypokalemia may account for some of these negative effects.⁴⁰ For these reasons, it is imperative that the long-term side effects of thiazides in stone formers, particularly regarding glucose intolerance, should also be prospectively evaluated.⁹

CONCLUSION

After a painful event of renal colic or surgical intervention for a stone, the patient has a strong motivation to avoid a repeat episode.³⁰ Therefore, the prevention of stone recurrence is an attractive strategy. Ideally, treatment recommendations should be based on the most reliable research available. When we look at the research before recommending a treatment, we are using evidence-based medicine.

However, evidence-based medicine should begin and end with the patient. Without sharing decision making, evidence may poorly translate into practice and improved outcomes.⁴¹ We can tell to our patients that applying current knowledge, MET for ureteral stones has a very limited efficacy, if any. Only one RCT, using a subgroup analysis demonstrated that tamsulosin might increase clearance of 5- to 10-mm, distal ureteric stones.¹² That a recent systematic review and meta-analysis found that further larger scale trials are required to analyze whether non-pharmacological interventions can increase urinary citrate levels and act

in kidney stone prevention.¹⁹ And finally, we can discuss with them that there is moderate-strength evidence that thiazides reduced stone recurrence. Nevertheless, in these trials from the 1980-1990s, the compliance was poor and the follow-up was very short.

The prevalence of nephrolithiasis is increasing. This finding has a significant impact not only on patient's morbidity but also on the cost of healthcare.¹ Very few potential new therapies have been introduced. Studies to identify optimal management of patients with recurrent kidney stone formation are both timely and necessary.⁴²

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