Review: Thiazide, citrate, or allopurinol reduces recurrence after ≥ 2 kidney stone episodes

Fink HA, Wilt TJ, Eidman KE, et al. ***Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians clinical guideline.*** *Ann Intern Med. 2013;158:535-43.*

Clinical impact ratings: GM ★★★★★★☆ Np ★★★★★☆☆

Question

In adults who have had ≥ 1 episode of kidney stones, what are the benefits and harms of interventions to prevent recurrence?

Review scope

Included studies compared dietary and/or pharmacologic interventions with placebo, usual care, no treatment, or other active treatment in adults ≥ 18 years of age who had a history of ≥ 1 kidney stone episode. Pharmacologic interventions included prescription medications, over-the-counter medications, and supplements available in the USA. Follow-up had to be ≥ 12 months for clinical outcomes and ≥ 3 months for adverse events. Studies of prescription medications not approved by the US Food and Drug Administration and studies of patients who had undergone lithotripsy within 90 days, unless they were stone-free, were excluded. Outcomes included radiographic, symptomatic, and composite (symptomatic or radiographic) stone recurrence.

Review methods

MEDLINE and Cochrane Library (to Sep 2012), Google Scholar, Web of Science, ClinicalTrials.gov, and reference lists of eligible randomized controlled trials (RCTs) and relevant systematic reviews were searched for RCTs published in English. 28 RCTs, with treatment duration ranging from 1 to 5 years, met the selection criteria. Study quality, assessed using Cochrane Collaboration criteria, was fair in 24 RCTs, good in 2 RCTs, and poor in 2 RCTs. Strength of evidence was assessed using methods developed by the Agency for Healthcare Research and Quality's Effective Health Care Program.

Main results

Moderate-strength evidence showed that, in patients with ≥ 2 previous calcium stones, thiazide, citrate, or allopurinol in patients who also had hyperuricemia or hyperuricosuria, usually in conjunction with increased fluid intake, reduced composite stone recurrence compared with control (Table). Low-strength evidence also suggested that increased fluid intake in patients with ≥ 1 previous calcium stone may reduce recurrence of composite stones (12% vs 27%, relative risk [RR] 0.45, 95% CI 0.24 to 0.84), and reduced soft drink intake in patients with ≥ 1 previous stone (type unspecified) may reduce recurrence of symptomatic stones (34% vs 41%, RR 0.83, CI 0.71 to 0.98). Other pharmacologic or dietary interventions did not reduce recurrence or were considered to have low or insufficient strength of evidence.

Pharmacologic treatment vs control for composite* stone recurrence in patients with ≥ 2 previous episodes of kidney stones†

Treatment	Number of trials (*n*)	Weighted event rates		At mean 1 to 5 y	
		Treatment	Control	RRR (95% CI)	NNT (CI)
Thiazide	5 (300)	29%	55%	48% (31 to 61)	4 (3 to 6)
Citrate	4 (197)	13%	52%	75% (56 to 86)	3 (3 to 4)
Allopurinol‡	2 (152)	33%	55%	41% (16 to 58)	5 (4 to 12)

**Composite of symptomatic or radiographic recurrence.*

†Abbreviations defined in Glossary. Weighted event rates, RRR, NNT, and CI calculated from control event rates and risk ratios in article using a random-effects model.

‡In patients with hyperuricosuria or hyperuricemia.

Conclusions

In adults with ≥ 2 previous kidney stone episodes, thiazide, citrate, or allopurinol, usually in conjunction with increased fluid intake, reduces composite stone recurrence. Evidence for other interventions is low or insufficient.

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For correspondence: Dr. H. A. Fink, Minneapolis Veterans Affairs Medical Center, Minneapolis, MN, USA. E-mail howard.fink@va.gov.

Commentary

Fink and colleagues thoroughly reviewed the evidence from RCTs evaluating therapies to prevent recurrent kidney stones. Given the relatively high prevalence of stones in the general population, there is a puzzling lack of adequate trials (only 28). None of the results are surprising. Potassium citrate and thiazides have long been known to prevent stones. However, the shortcomings of these trials include their relatively small size, short duration of follow-up and assessment of adverse events, and uncertainties about the populations to which the findings apply.

Although thiazides undoubtedly reduce stone recurrence, important long-term data about safety are lacking, and the current review did not address these issues. Although thiazides offer cardiovascular benefit to patients with hypertension, their adverse effects may lead to a different cost–benefit ratio in normotensive people with hypercalciuria. On the other hand, because hypercalciuria is strongly associated with decreased bone mineral density and higher fracture rates, thiazides may provide additional benefit related to increased bone mineral density.

No data show greater success of basing therapy on urine chemistry than empirical treatment based on stone composition. Similarly, no data show that titrating medications or dietary prescriptions based on urine chemistry is useful. Based on these findings, providers may choose not to collect chemistries, but many lithologists find the results of 24-hour urine testing useful for focusing patients on their own results, narrowing dietary prescriptions, and judging drug efficacy and adherence. Clearly more research is needed in this area.

The inclusion of only RCTs in the review is laudable. However, given the lack of sufficient rigorous data, physicians may also need to consider what is known from observational studies or our knowledge of urine chemistry. An obvious example is that only "low-strength evidence" shows the benefit of increased fluid intake, but data from non-RCTs strongly support higher urine volumes (1). More rigorous RCTs would be welcome to guide physicians on future management.

David S. Goldfarb, MD, FACP
New York Harbor VA Healthcare System and
New York University Langone Medical Center
New York, New York, USA

Reference

1. **Curhan GC, Willett WC, Rimm EB, Stampfer MJ.** A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. N Engl J Med. 1993;328:833-8.

