Effective Health Care Program

Genitourinary Conditions
Urinary Stones

Recurrent Nephrolithiasis in Adults: Comparative Effectiveness of Preventive Medical Strategies

Research Focus for Clinicians

In response to a request from the public, the Minnesota Evidence-based Practice Center, funded by AHRQ, performed a systematic review of the literature to examine the comparative effectiveness and adverse effects of interventions to prevent kidney stone recurrence in adults aged 18 years or older. Biochemical measurements for predicting the risk of stone recurrence after treatment were also evaluated. Studies that addressed acute pain management and treatment to promote expulsion of ureteral stones were excluded. This review focused on recurrent calcium stones in patients with or without residual stones or stone fragments. Many of the studies assessed in this review included patients with idiopathic calcium stones, although not all studies specified the etiology of kidney stones in the included population. For evaluating the relative effectiveness of interventions for preventing stone recurrence, only randomized controlled trials (RCTs) were included. For assessing adverse effects of the interventions, in addition to RCTs, prospective observational studies of at least 100 participants being treated for secondary prevention of kidney stones were included. A search of the clinical study literature published from 1948 through 2011 using predetermined inclusion and exclusion criteria yielded 28 RCTs that were included in the systematic review. The full report, listing all studies, is available at *www.effectivehealthcare.ahrq.gov/kidney-stones.cfm*. This summary, based on the full report of research evidence, is provided to inform discussions of options with patients and to assist in decisionmaking along with consideration of a patient's values and preferences. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background

Eighty percent of adults with kidney stones have calcium-based stones, with uric acid and struvite stones representing much of the remainder. Risk of stone formation may represent an interaction of both genetic and environmental factors. Data from large cohort studies suggest an association between the increased risk of stone formation and dietary factors such as low fluid intake, low calcium intake, high sodium intake, high animal protein intake, and high fructose intake. The risk of kidney stones may also be increased by medical conditions such as obesity, diabetes, primary hyperparathyroidism, and gout. Stones may be asymptomatic or may present with abdominal and flank pain, nausea and vomiting, urinary tract obstruction, and infection. Stone recurrence increases the risk of developing chronic kidney disease. Recurrence can be diagnosed by radiographic studies and/or by symptomatic stone recurrence. The 5-year recurrence rate in the absence of specific treatment is 35 to 50 percent.

Clinical uncertainty exists about the comparative effectiveness and adverse effects of pharmacological and dietary (e.g., increased fluids and adequate calcium) preventive treatments. Current guidelines recommend pretreatment biochemical analysis of blood and urine, but it is not clear if using the results of these analyses to tailor treatment is associated with better outcomes than empiric therapy. The authors of this systematic review examined the evidence around these uncertainties.

Conclusions

The published evidence regarding the effectiveness of dietary interventions to reduce the risk of calcium stone recurrence is limited. There is low-strength evidence that fluid intake to maintain urine excretion of at least 2 L per day may provide a clinically significant reduction in risk of stone recurrence. Similarly, low levels of evidence from a single study support abstaining from soft drinks or eliminating soft drinks containing only phosphoric acid but not citric acid in men who frequently consume such drinks. A normal-calcium (1,200 mg/day), low-sodium, low-animal protein diet may reduce the risk for stone recurrence, but the independent effects of increasing dietary calcium or reducing dietary sodium or animal protein have not been determined. Diets with high fiber or reduced animal protein as solitary interventions may not help prevent stone recurrence. The effectiveness of other dietary interventions is not clear.

When added to increased fluid intake, thiazide diuretics, citrate, and allopurinol pharmacotherapy each significantly decreased the risk of recurrent calcium kidney stones more than increased fluid intake alone. Allopurinol treatment reduced the rate of stone recurrence for patients with elevated blood or urine levels of uric acid. Thiazides or citrates may be preferred initial therapy over allopurinol in patients with calcium stones and no hyperuricosuria or hyperuricemia. Patients receiving pharmacological interventions may experience adverse effects that lead to withdrawal from treatment.

Other than allopurinol treatment in patients with high levels of blood or urine uric acid, clinical studies have not clearly established the general utility of baseline blood and 24-hour urine biochemical measures. No RCTs reported and prospectively compared subsequent stone recurrence

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Conclusions (*Continued*)

outcomes between treatments stratified by followup biochemistry levels or by changes in these measures from pretreatment baseline values.

Regarding applicability, nearly all trials were limited to patients with a history of calcium stones and were conducted primarily in young to middle-aged men. Many trials excluded participants with biochemical abnormalities, and nearly all excluded individuals with specific conditions that could predispose them to stone formation. Applicability is also limited by the absence of reported data on participant characteristics including race, body morphometry, and comorbid conditions that increase the risk for kidney stones or affect treatment outcomes.

Clinical Bottom Line

Dietary Interventions

Benefits	Adverse Effects
■ A limited body of evidence suggests that dietary interventions may reduce the risk of stone recurrence (see Table 1 on the next page for details). ●○○ ■ Neither high-fiber nor reduced-animal protein diets as isolated interventions had a statistically significant effect on stone recurrence. ●○○	■ Adverse effects, as reflected by withdrawals for any cause, were low in trials evaluating increased fluid intake but high in long-term trials evaluating other dietary interventions. No significant differences in withdrawals between intervention and control groups were reported in these trials.

Pharmacological Interventions

Benefits	Adverse Effects
Trials were designed to evaluate the effects of pharmacological agents given in addition to standard dietary recommendations (e.g., increase fluids, limit oxalate-containing foods, limit sodium). ■ Thiazide diuretics, citrate, and allopurinol each reduce the risk of calcium stone recurrence (composite endpoint*). ●●○ □ Thiazide diuretics: ARR = 29 percent, NNT = 3 (RR = 0.53 [95% CI 0.41 to 0.68]) - Hydrochlorothiazide, chlorthalidone, and indapamide each reduce the risk of recurrent stones, but no trial directly compared thiazide agents to each other. - No trial directly compared different dosages of pharmacological agents, and no trial assessed the lower thiazide doses often used to treat hypertension (12.5 to 25 mg per day for hydrochlorothiazide and < 25 mg per day for chlorthalidone). □ Citrate: ARR = 41 percent, NNT = 3 (RR = 0.25 [95% CI, 0.14 to 0.44]) □ Allopurinol (in patients with elevated blood or urine uric acid): ARR = 22 percent, NNT = 5 (RR = 0.59 [95% CI, 0.42 to 0.84]) ■ There is no additional benefit (composite endpoint*) from adding citrate to thiazide in patients with calcium stones, 35 percent of whom had hypercalciuria and 15 percent of whom had hypocitraturia. ●○○ ■ Treatment with magnesium did not reduce the risk (composite endpoint*) of stone recurrence when compared with placebo. No statistically significant difference in the risk of recurrence was observed. ●○○ ■ The evidence about acetohydroxamic acid treatment to prevent stone recurrence (radiographic) in patients with chronic urinary tract infections and struvite stones is insufficient to permit conclusions (○○○), which does not exclude that the drug does not work. Evidence from three RCTs suggests that there is reduction in stone growth with acetohydroxamic acid treatment.	■ When compared with participants given placebo or control treatments, patients assigned to thiazide, citrate, or acetohydroxamic acid were more likely to withdraw from trials and to withdraw due to adverse events. ■ Participants treated with allopurinol were not more likely than control group participants to withdraw from trials overall or to withdraw due to adverse events. ■ Patients given high-dose magnesium were more likely to withdraw due to adverse events (all due to diarrhea) when compared with placebo groups. ■ Specific adverse events were poorly reported. U.S. Food and Drug Administration labels should be consulted when using these agents.

* Composite endpoint refers to stones detected by either symptoms or scheduled radiographs.
ARR = absolute risk reduction; NNT = number needed to treat; RCT = randomized controlled trial; RR = relative risk; 95% CI = 95-percent confidence interval

Strength of Evidence Scale

High:	●●●	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate:	●●○	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low:	●○○	Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient:	○○○	Evidence either is unavailable or does not permit a conclusion.

Clinical Bottom Line (*Continued*)

Baseline and Followup Blood and Urine Biochemical Evaluations To Predict Stone Recurrence*

Baseline Biochemical Evaluations	Followup Biochemical Evaluations
■ Almost no RCTs reported stone recurrence outcomes between treatments for subgroups stratified by baseline biochemistry levels. In comparisons between studies, results were mixed about whether specific baseline biochemical measures predicted the effectiveness of diet or pharmacological treatment relative to control in reducing risk of stone recurrence. ■ In two RCTs limited to patients with calcium stones and hyperuricosuria or hyperuricemia, those randomized to allopurinol versus a control group had a significantly lower risk of recurrent stones using composite endpoints** (33.3% vs. 55.4%; RR, 0.59 [95% CI, 0.42 to 0.84]), whereas the symptomatic stone recurrence rate did not appear lower with allopurinol in trials of participants unselected for high uric acid levels. ■ Limited evidence suggests that baseline calcium, oxalate, and citrate measures do not appear to predict efficacy of diet and pharmacological interventions on recurrent stone outcomes. ■ Otherwise, the evidence is too limited to determine the role of baseline urine measures—including magnesium, phosphate, potassium, pH, calcium-oxalate supersaturation, calcium phosphate supersaturation, or uric acid supersaturation—in predicting treatment efficacy or stone recurrence.	■ No RCTs reported and prospectively compared subsequent stone recurrence outcomes between treatments stratified by followup biochemistry levels or by changes in these measures from pretreatment baseline. ■ Two RCTs involving increased fluid intake and a multicomponent diet, respectively, reported significant reductions in urine calcium-oxalate, uric acid, and calcium-phosphate supersaturation at 1 year or later after baseline and a significantly reduced risk of recurrent stones over 5 years of followup. However, neither study formally tested these results for possible associations. ■ No eligible pharmacological RCT reported followup urine supersaturation levels. Thus, no RCT data were available about whether changes in urine supersaturation measures predict reduced risk of recurrent stones with drug treatment. ■ Evidence from three dietary RCTs suggests that followup measurement of the urine calcium level after treatment is unlikely to be a reliable predictor of treatment effectiveness for reducing the risk of stone recurrence. ■ Evidence from six thiazide RCTs suggests that followup measurement of the urine calcium level after thiazide treatment may not be a reliable predictor of treatment effectiveness for reducing the risk of stone recurrence.

* The strength of evidence in support of these conclusions was not rated.
** Composite endpoint refers to stones detected by either symptoms or scheduled radiographs.
RCT = randomized controlled trial; RR = relative risk; 95% CI = 95-percent confidence interval

Table 1. Effects of Dietary Interventions on Risk of Urinary Stone Recurrence

Intervention	Comparator	Mode of Detection	ARR	NNT	RR (95% CI)	Strength of Evidence
Increasing fluids to maintain urine output > 2 L per day (for individuals with a single previous calcium stone episode)	No increase in fluids	Composite*	15%	7	0.45 (0.24 to 0.84)	●○○
Eliminating soft drinks (based on a single study in men)	No advice to reduce intake of soft drinks	Symptomatic	7%	14	0.83 (0.71 to 0.98)	●○○
Eliminating soft drinks acidified solely with phosphoric acid but not citric acid: a subgroup analysis of participants who frequently consumed such soft drinks			16%	6	0.65 (0.49 to 0.87)	●○○
Low-animal protein, low-sodium, decreased-oxalate, increased-water, and normal-calcium diet†	Low calcium, decreased oxalate, and increased water intake	Composite	18%	6	0.52 (0.29 to 0.95)	●○○
Low-animal protein, high-fiber, increased-bran, low-purine, adequate-calcium, and increased-fluid diet	Adequate calcium and increased fluid	Composite	-20%	5	5.88 (1.39 to 24.92)	●○○
Tailored diet based on a metabolic evaluation**	Empirical dietary recommendations	Composite	13%	8	0.32 (0.14 to 0.74)	●○○

* Composite endpoint refers to stones detected by either symptoms or scheduled radiographs.
† The recommended level of dietary calcium intake in this study was 1,200 mg per day.
** Changes in risk according to a specific metabolic abnormality and specific dietary recommendations were not reported.
ARR = absolute risk reduction: the difference in risk between the control group and the treatment group; NNT = number needed to treat: the number of patients to be treated to find the benefit in one patient more than in the control group; RR = relative risk; 95% CI = 95-percent confidence interval

Gaps in Knowledge

A review of RCTs to assess the benefits and of RCTs and observational studies to assess the adverse effects revealed a number of gaps in knowledge as reflected in these particular types of studies.

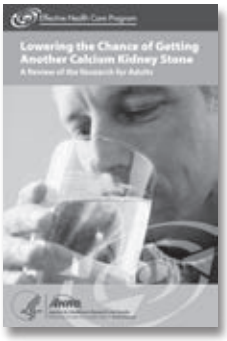
- There is no direct evidence from RCTs about whether diets that increase calcium or lower sodium, oxalate, or purine (independent of other dietary components) reduce the risk of recurrent kidney stones.
- It is unknown whether the efficacy of dietary interventions differs as a function of participant characteristics.
- Direct comparisons of dietary interventions to each other, of pharmacological interventions to each other, and between these two types of interventions are rare or absent.
- The effects of dietary and pharmacological interventions on stone types other than calcium stones, and of acetohydroxamic acid for other than struvite stones, is unexamined in RCTs that report the effects of these treatments on the risk of recurrent stones.
- No trial assessed the effectiveness of lower thiazide doses, a drug class often used to treat hypertension (hydrochlorothiazide 12.5 to 25 mg per day and chlorthalidone < 25 mg per day), for reducing the risk of recurrent stones.
- Studies are needed to formally test whether the risk for stone recurrence after either dietary or pharmacological treatment can be stratified according to blood and urine biochemical measures either at baseline or at followup.

What To Discuss With Your Patients

- That kidney stones have a high chance of recurring if not managed properly
- The importance of maintaining daily fluid intake to achieve urine output of > 2 L per day
- The benefits and adverse effects of medicines for preventing kidney stone recurrence
- Dietary changes that may be beneficial in reducing the risk of kidney stones (i.e., eliminating soft drinks acidified solely with phosphoric acid, increasing calcium-rich foods to achieve the recommended daily intake, and limiting oxalate-containing foods)

Resource for Patients

Lowering the Chance of Getting Another Calcium Kidney Stone, A Review of the Research for Adults is a free companion to this clinician research summary. It can help patients talk with their health care professionals about the many options for treatment. It provides information about:



- The causes of kidney stones and the risk of recurrence
- The role of dietary therapies in preventing kidney stones
- The benefits and adverse effects of medicines that can be added to dietary therapies

Ordering Information

For electronic copies of *Lowering the Chance of Getting Another Calcium Kidney Stone, A Review of the Research for Adults*, this clinician research summary, and the full systematic review, visit *www.effectivehealthcare.ahrq.gov/kidney-stones.cfm*. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

Source

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