Published in final edited form as:

Eur Urol. 2009 July ; 56(1): 72–80. doi:10.1016/j.eururo.2009.03.031.

Diet, Fluid, or Supplements for Secondary Prevention of Nephrolithiasis: A Systematic Review and Meta-Analysis of Randomized Trials

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Abstract

Context—Although numerous trials have evaluated efficacy of diet, fluid, or supplement interventions for secondary prevention of nephrolithiasis, few are included in previous systematic reviews or referenced in recent nephrolithiasis management guidelines.

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Analysis and interpretation of data: Fink, MacDonald, Monga, Wilt

Drafting of the manuscript: Fink, Akornor, Garimella

Critical revision of the manuscript for important intellectual content: Fink, Garimella,

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Statistical analysis: none

Obtaining funding: Wilt, Fink

Administrative, technical, or material support: none

Supervision: none

Other (specify): none

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Take-home message

High water intake reduces recurrent nephrolithiasis risk, and reduced soft drink intake may prevent recurrent colic in men with high baseline soft drink consumption. Data on other diet interventions are inconclusive, although limited data suggest possible benefit from dietary calcium.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: none

The views expressed in this article are those of the authors and do not necessarily represent the views of the US Department of Veterans Affairs.

Objective—To determine efficacy and safety of diet, fluid, or supplement interventions for secondary prevention of nephrolithiasis.

Evidence acquisition—Systematic review and meta-analysis of trials published January 1950 to March 2008. Sources included Medline and bibliographies of retrieved articles. Eligible trials included adults with a history of nephrolithiasis; compared diet, fluids, or supplements with control; compared relevant outcomes between randomized groups (eg, stone recurrence); had ≥ 3 mo follow-up; and were published in the English language. Data were extracted on participant and trial characteristics, including study methodologic quality.

Evidence synthesis—Eight trials were eligible ($n = 1855$ participants). Study quality was mixed. In two trials, water intake >2 l/d or fluids to achieve urine output >2.5 l/d reduced stone recurrence (relative risk: 0.39; 95% confidence interval: 0.19–0.80). In one trial, fewer high soft drink consumers assigned to reduced intake had renal colic than controls (34% vs 41%, $p = 0.023$). Content and results of multicomponent dietary interventions were heterogeneous; in one trial, fewer participants assigned increased dietary calcium, low animal protein, and low sodium had stone recurrence versus controls (20% vs 38%, $p = 0.03$), while in another trial, more participants assigned diets that included low animal protein, high fruit and fiber, and low purine had recurrent stones than controls (30% vs 4%, $p = 0.004$). No trials examined the independent effect of altering dietary calcium, sodium, animal protein, fruit and fiber, purine, oxalate, or potassium. Two trials showed no benefit of supplements over control treatment. Adverse event reporting was poor.

Conclusions—High fluid intake decreased risk of recurrent nephrolithiasis. Reduced soft drink intake lowered risk in patients with high baseline consumption. Data for other dietary interventions were inconclusive, although limited data suggest possible benefit from dietary calcium.

1. Introduction

The lifetime prevalence of nephrolithiasis has been estimated at 13% among men and at 7% among women [1,2], with conflicting data regarding whether prevalence is increasing [1–3]. Although stones may be asymptomatic, potential consequences include renal colic, urinary tract obstruction, infection, hospitalizations, and procedure-related morbidity. Following an initial stone event, the spontaneous 5-yr recurrence rate is 35–50% [4].

In large observational studies, several modifiable factors have been associated with increased risk of nephrolithiasis, including low fluid intake, low dietary calcium, and low dietary potassium, while results for diets with increased animal protein and increased sodium have been mixed [5,6]. Although a number of trials have evaluated the efficacy of diet, fluid, or supplement interventions in reducing risk of recurrence, few have been included in previous systematic reviews [7,8] or have been referenced in recent nephrolithiasis management guidelines [9,10]. Therefore, we conducted this systematic review and meta-analysis to clarify the evidence on the benefits and the adverse effects of diet, fluids, and supplement treatments for secondary prevention of nephrolithiasis.

2. Evidence acquisition

2.1. Literature search

We searched Medline (January 1950 to March 2008) using the following terms: *urolithiasis* and *controlled clinical trial* or *randomized clinical trial* or *randomized controlled trial* or *systematic reviews* or *meta-analysis*. Bibliographies of retrieved trials and review articles also were examined.

2.2. Selection criteria

A trial was eligible for inclusion if it met the following criteria: (1) it was composed of community-dwelling participants aged ≥ 18 yr with at least one prior resolved episode of renal colic; (2) it was randomized; (3) it compared a diet, fluid, or supplement intervention with a control; (4) it compared relevant outcomes between randomized groups for secondary prevention of nephrolithiasis (eg, stone recurrence); (5) it had at least a 3-mo follow-up; and (6) it was published in English. Acute treatment trials were excluded. For each trial, two reviewers (HAF, AHC, and/or IRR) independently assessed eligibility, with differences resolved by discussion.

2.3. Data extraction and outcome measures

Data retrieved on trial characteristics included patient demographics and trial entrance criteria, (ie, stone characteristics, size, number, and history of past stone episodes). Dropouts, treatment efficacy, and adverse events were extracted by two independent reviewers (HAF, AHC, and/or IRR) in a standardized fashion. Discrepancies were unusual and were resolved by discussion. The following trial efficacy outcomes were considered for inclusion in this review: (1) recurrent renal colic; (2) recurrent asymptomatic renal calculi; and/or (3) growth or reduction in size of prevalent renal calculi.

2.4. Assessment of methodologic quality

Studies were assessed for quality of concealment of randomized treatment allocation and were assigned scores from 1 for poorest quality to 3 for best quality [11]. Additionally, we assessed whether trial participants and investigators were masked to treatment, whether trials used an intention-to-treat analysis, and the percentage of participants who withdrew or were lost to follow-up.

2.5. Statistical analysis

For assessment of efficacy and adverse-event outcomes, we determined the percentage of participants achieving each outcome according to assigned procedure. Where interventions and outcome measures were comparable between trials, we calculated weighted relative risks (RRs) and their 95% confidence intervals (CIs) using Review Manager (RevMan) v.4.1 software [12]. RRs were estimated using random effects meta-analyses, and results were tested for heterogeneity at a significance level of $p < 0.10$. When we considered trials too heterogeneous in patient characteristics, interventions, and/or outcome measures to allow statistical pooling, we described the magnitude of observed effects across different outcome measures according to treatment intervention.

3. Evidence synthesis

3.1. Study selection

We identified 579 citations via our Medline search. After review of titles and abstracts, we retrieved 28 articles for detailed review, of which 8 met inclusion criteria. No additional references identified from bibliographies of retrieved trials and review articles met inclusion criteria.

3.2. Trial characteristics

Eight trials of diet [13–18] or supplement interventions [19,20] met eligibility criteria and were included in this review (1855 total participants; number of participants per trial: 45–1010). All trials were published in peer-reviewed English-language journals and indicated that they were randomized, although only one reported an adequate method of random allocation and concealment of treatment assignment (Table 1) [14]. All trials used a parallel

treatment group design. Treatment duration ranged from 3 mo to 60 mo. Outcome assessors were masked to participant treatment assignment in four of eight trials [14,16,17,20], while participants were masked in only one trial [19]. Five trials included all randomized participants in outcomes analyses [14,16–19].

Four trials reported a composite outcome of either symptomatic stone passage or radiographic detection by scheduled x-rays and/or ultrasounds [13–16], one trial reported separate outcomes for symptomatic stones and radiographically detected stones [19], one trial reported symptomatic stone episodes only [17], and one trial reported radiographic detection only [18]. Additionally, four trials reported results for change in stone size [15,18–20].

3.3. Participant characteristics

Trial participants were predominately young (range of mean ages: 38–45.1 yr; six trials reporting) and male (85.0%) (Table 2). Only one trial reported data on participant race [16], and none reported comorbidity data. Most studies were limited to participants with calcium stones and excluded participants with known conditions associated with calcium nephrolithiasis [13–16,18,19]. Four trials included only participants with a single past episode of nephrolithiasis [13,15,16,18], one trial included only those with multiple past episodes [14], and one trial included both groups [17]. Two trials included only participants with residual stones [19,20], two trials included only participants without residual stones or fragments [13,16], three trials included both groups [14,15,18], and one trial provided no data [17].

3.4. Efficacy outcomes

3.4.1. Increased fluid intake—Two trials found that increased fluid intake was associated with a significant reduction in stone recurrence (Table 3) [13,18]. In one study, participants were randomized to >2 l/d of water intake versus no treatment for 5 yr [13]. Those allocated to high water intake were significantly less likely to have stone recurrence (12% vs 27%, $p = 0.008$). In the second study, participants who had undergone shockwave lithotripsy were randomized to increased fluid intake to achieve urine output of >2.5 l/d or no treatment for 2–3 yr [18]. Among stone-free participants, stone recurrence occurred in 8% of patients randomized to increased fluid compared with 56% of those allocated to no treatment ($p < 0.01$). Among participants with residual stone fragments, 46% of patients randomized to increased fluid were stone free at follow-up compared with 18% of patients allocated to no treatment ($p < 0.01$). Among participants from both trials who were stone free at baseline, increased fluid reduced recurrence risk by 61% (RR: 0.39; 95% CI: 0.19–0.80).

3.4.2. Decreased soft drink intake—One trial, conducted in stone-forming men with a baseline soft drink consumption >160 ml/d, reported a reduction in self-reported, physician-confirmed renal colic episodes in those randomized to advice to abstain from soft drink intake or no intervention for 3 yr (34% vs 41%, $p = 0.023$) [17]. Total fluid intake was similar in both groups. Subgroup analysis found that benefit appeared restricted to participants whose most frequently consumed soft drink at baseline was acidified by phosphoric acid and not by citric acid.

3.4.3. Combination diets—Three trials evaluated the efficacy of a multicomponent dietary intervention for reduction of recurrent nephrolithiasis and reported conflicting results. In one study, participants were randomized to a diet with a low quantity of animal protein (56–64 gm/d), high fruit content, high vegetable and whole grain content, increased bran content (0.25 cup per day), and low purine content (75 mg/d) or to a control diet for 2

yr [16]. Both groups were advised to consume two dairy servings (or calcium carbonate supplements) and six to eight glasses of liquid daily. Thirty percent of participants randomized to the multicomponent dietary intervention experienced stone recurrence versus 4% of those allocated to the control diet ($p = 0.004$). In a subgroup analysis, incidence of stone recurrence appeared greater in participants who best complied with low-protein diet recommendations. In a second trial, participants were randomized to a limited metabolic evaluation with general diet recommendations or an extensive metabolic evaluation and tailored diet [15]. Among participants who underwent the extensive evaluation, those identified with hypercalcuria were assigned restricted animal protein and 750–1000 mg/d of dietary calcium. Those identified with hyperuricosuria or hyperuricemia were assigned a low-purine diet and restricted to 80 gm/d of meat products with 1–2 meatless days per week. Those identified with hyperoxaluria were assigned a diet with restricted oxalate intake, regular dairy intake, lemons, and increased fiber intake. Those identified with magnesium deficiency were assigned increased fiber, regular dairy intake, and high-magnesium mineral water. Those identified with hypocitraturia were assigned a diet with restricted animal protein, one to two servings of lemons or orange juice per day, and increased fruit and vegetables. General diet recommendations included 750–1000 mg/d of calcium, 100–120 gm/d of animal protein, oxalate restriction, increased fiber intake, and “moderate” sodium intake. Fewer participants randomized to the extensive evaluation and tailored diet had recurrent stones (6% vs 19%, $p < 0.01$); however, results were not reported separately for any metabolic or tailored diet subgroup. In a third trial, men were randomized to high dietary calcium (1200 mg/d), low animal protein (52 gm/d), and low sodium (50 mmol/d) or a control diet including low calcium (400 mg/d) for 5 yr [14]. Both groups were advised to drink 2–3 l of water per day and to decrease oxalate intake. Twenty percent of participants randomized to diets with high calcium, low animal protein, and low sodium had recurrent stones compared with 38% of those allocated to the control diet ($p = 0.03$).

3.4.4. Other dietary interventions—No trials evaluated the efficacy of diets with altered calcium, low sodium, low animal protein, increased fruit and fiber, low purine, low oxalate, or increased potassium independent of other diet changes. Results from multicomponent dietary intervention trials (see section 3.4.3.) suggested that diets including regular calcium intake may lower stone recurrence compared with a general diet or a low-calcium diet [14,15]. In single trials, participants assigned a multicomponent diet that included low dietary sodium intake [14] or low oxalate [15] had less frequent stone recurrence than those randomized to the control diet. Multicomponent dietary intervention trials that included low animal protein [14–16], increased fruit and fiber [15,16], and/or low purine intake [15,16] reported mixed results associated with each of these components.

3.4.5. Dietary supplements—Two trials that evaluated dietary supplements showed no benefit over control treatment [19,20]. In one trial, participants with a history of nephrolithiasis and with radiographic stones present at baseline were randomized to *Orthosiphon grandiflorus* extract 2.5 gm in tea twice daily or to sodium potassium citrate 5–10 gm three times daily for 18 mo [20]. Based on serial ultrasounds, mean annualized reduction in stone diameter at 18 mo was approximately 40% in both groups (p was not significant). In the second trial, participants with at least one calcium renal stone based on both x-ray and ultrasound were randomized to *Phyllanthus niruri* extract capsules 450 mg three times daily or to placebo for 3 mo [19]. Among those randomized to *Phyllanthus niruri*, 12% of subjects passed a stone during the study compared with 14% of those allocated to placebo ($p = \text{NS}$). Additionally, there was no between-group difference in the number or size of ultrasound-detected calculi at the end of the study.

3.5. Compliance with assigned treatment

One trial assessed patient compliance by serial administration of a food frequency questionnaire [16], another assessed patient compliance by repeated questionnaires on beverage intake [17], and a third stated that compliance with fluid intake was good in most participants but provided no supporting data [18]. Six trials assessed compliance and/or response to treatment with follow-up measures of blood chemistry and/or urine chemistry [13–16,19,20], including one trial with only end-of-treatment follow-up [19] and two that adjusted supplement dose [20] or repeated diet counseling based on interim biochemistry results [15].

3.6. Adverse events

3.6.1. Withdrawals—Dropouts in trials averaged 7% (range: 0–21%), with 2% of randomized participants withdrawing due to adverse events (range: 0–10%; five trials reporting). There were few data on reasons for withdrawal. In one study, among participants assigned to the low-calcium diet, two died and seven withdrew due to hypertension; of participants assigned to a diet with high calcium, low protein, and low sodium, two were lost to follow-up and six withdrew, with three withdrawals unwilling to continue and one each attributed to stroke, gout, and hypertension [14]. In a second study, two participants (9%) assigned to *Orthosiphon grandiflorus* withdrew because of loss of interest, and five participants (20%) assigned to sodium potassium citrate withdrew due to fatigue and loss of appetite [20].

3.6.2. Side effects—Only two trials reported data on adverse effects [14,20]. In one trial, hypertension occurred in 2% of participants randomized to the diet with low protein, low sodium, and high calcium compared with 12% of participants who were assigned to the low-calcium diet [14]. In a second trial, no participants assigned to *Orthosiphon grandiflorus* reported adverse effects, while 35% of those assigned to sodium potassium citrate supplementation reported fatigue or loss of appetite [20].

4. Conclusions

Our systematic review of randomized controlled trials (RCTs) found that high water intake lowered long-term risk of nephrolithiasis recurrence by approximately 60% and that among men with high baseline soft drink intake, reduced soft drink consumption modestly lowered risk of recurrent renal colic. Results from one trial suggested that when added to increased water intake, a diet including higher calcium, lower animal protein, and lower sodium reduced stone risk compared with a low-calcium diet. Results from other multicomponent diet intervention trials also suggested that diets including regular calcium may lower recurrence risk but did not provide further support for the efficacy of diets including low sodium, and these results suggested the possibility that lower animal protein may increase risk of stone recurrence. Furthermore, we found no trials that examined the independent effect of altering dietary intake of calcium, sodium, animal protein, fruit and fiber, purine, oxalate, or any other individual dietary element on risk of stone recurrence. There was no evidence for benefit of specific dietary supplements for prevention of stone recurrence. Adverse event reporting was poor.

Our finding that increased water or fluid intake is protective against recurrent nephrolithiasis is consistent with observational data [6] and with research demonstrating that urinary dilution in vitro and in vivo reduces urinary supersaturation of calcium phosphate, calcium oxalate, and monosodium urate [21]. Increased fluid intake also may help prevent nephrolithiasis by increasing crystalline-product transit through the nephron, thus decreasing contact time with potential adsorptive surfaces [22]. Given the consistent findings of benefit,

albeit from only two trials, there appears to be sufficient evidence to recommend increased fluid intake in patients with a history of nephrolithiasis, either by daily water intake of >2 liters or by daily urine output of >2.5 liters.

Trial findings that reduction in soft drink intake significantly lowered risk of recurrent renal colic in men with high baseline levels of soft drink consumption, particularly those whose drinks were acidified solely by phosphoric acid, did not appear to be explained by a compensatory increase in consumption of other liquids. Two large prospective cohort studies reported no increased risk of nephrolithiasis associated with any type of soft drink consumption after adjusting results for total fluid intake and other factors [23,24]. Based on trial results, nephrolithiasis patients with high intake of phosphoric acid (via acidified soft drinks) may be advised to minimize their soft drink consumption while maintaining adequate total fluid intake.

In prior observational data, an inverse association has been reported between dietary calcium intake and risk of nephrolithiasis [5,6]. The proposed mechanism for this effect is that adequate dietary calcium intake leads to binding of oxalate in the intestine, leading to a lower risk of hyperoxaluria; however, no trial studied the independent effect of regular dietary calcium on stone recurrence. One trial that compared a multicomponent diet including 1200 mg/d of calcium with a low-calcium diet reported a substantial reduction in stone recurrence. While a second trial that included regular or increased dietary calcium as part of a multicomponent diet reported reduced stone recurrence risk compared with a group that received general diet recommendations, the general diet recommendations included 750–1000 mg/d of dietary calcium, so that both treatment groups were assigned diets with daily calcium intake greater than their average baseline intake. Furthermore, actual dietary calcium intake during treatment was not reported [15]. Therefore, it is possible that results in this second trial were not attributable to dietary calcium intake or, conversely, that observed outcome differences underestimated the benefit of regular dietary calcium intake relative to that of lower calcium intake. Although trial evidence for the beneficial effect of dietary calcium is limited and indirect, it seems reasonable for patients with a history of nephrolithiasis to maintain at least regular dietary calcium intake. Because the individual elements composing the different multicomponent dietary intervention trials were heterogeneous, and their results were conflicting in some aspects, conclusions about their efficacy for reducing risk of stone recurrence should be drawn cautiously. In one trial, for example, risk of stone recurrence was lower in participants assigned to regular dietary calcium, low sodium, and low animal protein versus a low-calcium diet. Because both groups were advised to increase water and to decrease oxalate intake, the observed treatment benefit appeared to be additional to any from these cointerventions; however, the specific impact of lowering sodium and/or animal protein intake on these results was uncertain. Although high sodium intake increases urine pH and urinary calcium excretion and reduces urinary citrate [25], associations with increased risk of stones in observational studies are inconsistent [5,6], and no other trials have examined the effect of lowering dietary sodium on risk of stone recurrence, even in combination with other diet changes. Therefore, at this time, no conclusion can be drawn regarding the efficacy of dietary sodium restriction for prevention of stone recurrence. A second multicomponent diet trial, in which both treatment groups were assigned increased fluid intake and dietary calcium, showed a lower risk of recurrence in the control group and a much greater risk of stone recurrence in participants assigned to lower animal protein, increased fruit, whole grains, and bran, and lower purines. Despite data indicating favorable effects of lower animal protein on urinary constituents [26–28], associations between animal protein intake and stone risk in observational studies are inconsistent [5,6]. Based on results from randomized trials, it is unclear whether a diet low in animal protein will, when combined with high water intake and regular dietary calcium intake, decrease, have no effect on, or will even increase risk of stone recurrence. It

cannot be determined whether addition of increased fruit, whole grains, bran, and decreased purines increased stone-recurrence risk in the second trial, but at this time there is insufficient evidence to support their inclusion in a diet to reduce risk of stone recurrence. For a third multicomponent diet trial, because it reported only overall results from a comparison between groups assigned to a comprehensive metabolic evaluation and tailored diet versus a limited evaluation and general diet, it is not possible to separate out the beneficial or adverse effects of any specific dietary element or multicomponent diet, overall or in any metabolic subgroup. Inconsistent results from other trials suggest that not all components of the comprehensive metabolic evaluation and tailored diet were likely to be contributing to a reduction in recurrent stone risk.

There are few RCT data on the efficacy of supplements, with neither of two eligible trials suggesting benefit. Although mixed results from observational studies have suggested that calcium supplements may increase stone recurrence risk [5,6], we identified no RCTs that randomized nephrolithiasis participants to calcium supplements compared with control for prevention of recurrent stones. A systematic review of RCTs of calcium supplementation, mostly performed in older women to prevent fractures or bone loss, reported no increased rate of stone events among those allocated to calcium supplementation [29].

The current review is limited by the available evidence. First, heterogeneity in patient populations, treatment interventions, and methods of recurrent stone ascertainment hindered our ability to compare efficacy outcomes among trials and to explain apparently mixed results for specific individual dietary elements and multicomponent diets. Second, though one trial tested a general strategy of extensive metabolic evaluation and tailored diet versus limited evaluation and a general diet, there were no trials that evaluated the efficacy of a diet, fluid, or supplement intervention versus control within any specific metabolic subgroups, such as in patients with hyperoxaluria, hyperuricosuria or hyperuricemia, or hypercalcuria. Third, the small size of most trials limits the confidence that can be placed in efficacy estimates. Fourth, few adverse effects data were reported, though the relatively low withdrawal rates suggested that the interventions were tolerated. Finally, trials were predominately performed in younger men with calcium stones, so the generalizability of results to other patient populations is not certain.

In conclusion, evidence from this systematic review of RCTs indicates that high water intake reduces risk of recurrent nephrolithiasis and that reduction of soft drink intake may prevent recurrent colic in men with high baseline level of soft drink consumption. Limited data suggest that regular dietary calcium may provide additional benefit. Data on other diet interventions are inconclusive. Future trials are needed to better clarify whether there is additional benefit from reducing dietary intake of animal protein, sodium, or oxalate, and from increasing dietary calcium, potassium, or intake of fruit and/or fiber. Consensus should be sought regarding the definition of clinically meaningful end points, so that efficacy outcomes are standardized across trials. Adverse effects and patient compliance should be better tracked to provide additional insight regarding potential implementation of therapies shown to be effective.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support and role of the sponsor: This study was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (grant no. DKR01 063300-01A2). Additional support was provided by the Center for Chronic Disease Outcomes Research and the Cochrane Review Group in Prostatic Diseases and Urologic

Cancers, Veterans Affairs Medical Center, Minneapolis. The funding agency played no role in study design, data acquisition, and abstraction, analysis or preparation of the manuscript.

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Table 1

Quality of included trials

Study	Adequacy of concealment of random allocation	Blinding	Intention-to-treat analysis	Dropouts adequately described
Dietary Studies				
Shuster et al [17]	Unclear: not specified	Participants: no Outcome assessors: yes Investigators: not specified	Yes	Yes
Borghi et al [14]	Unclear: not specified	Participants: no Outcome assessors: not specified Investigators: not specified	No	Yes
Hiatt et al [16]	Unclear: not specified	Participants: no Outcome assessors: yes Investigators: not specified	Yes	Yes
Kocvara et al [15]	Unclear: not specified	Participants: no Outcome assessors: not specified Investigators: no *	No	No
Borghi et al [13]	Adequate: consecutively numbered, sealed, opaque envelopes	Participants: no Outcome assessors: yes Investigators: not specified	Yes	Yes
Sarica et al [18]	Unclear: not specified	Participants: no Outcome assessors: not specified Investigators: not specified	Yes	No dropouts
Supplement studies				
Premgamone et al [20]	Unclear: not specified	Participants: no Outcome assessors: yes Investigators: not specified	No	Yes
Nishiura et al [19]	Unclear: not specified	Participants: yes Outcome assessors: unclear [§] Investigators: unclear [§]	Yes	No dropouts

* Diet counseling was adjusted during the trial based on results of biochemical testing during treatment follow-up.

[§]The researchers reported that “all patients were randomized to receive *P. niruri* or a placebo and treated in a double-blind fashion,” although no further information was provided with respect to blinding of outcome assessors or investigators.

Table 2

Trial, participant, and stone characteristics

Study	No. of participants randomized, no. of withdrawals (n)	Duration, mo	1. Intervention regimen 2. Control regimen	Participant characteristics	Stone characteristics
<i>Dietary studies</i>					
Shuster et al [17]	1009 (72)	36	1. Advice to avoid soft drinks (n = 504) 2. No intervention (n = 505)	American men (100%); mean age: 43 yr; exclusions: soft drink consumption <160 ml/d	Physician-confirmed nephrolithiasis episode (first episode 37%, recurrent 63%); no data on presence/absence of residual stone fragments; all stone subtypes
Borghi et al [13]	220 (21)	60	1. High water intake, >2 l/d (n = 110) 2. No treatment (n = 110)	Italian men (67%) and women (33%) of 199 completing trial; mean age: 41 yr; exclusions: residual stone, hypertension, metabolic condition requiring regular dietary measures or drug therapy	First nephrolithiasis episode; 0% with residual stone/fragments; calcium oxalate stone
Hiatt et al [16]	102 (24)	24	1. Low animal protein (56–64 gm/d); high fruit, vegetables and whole grains; increased bran (0.25 cup per day); low purine (75 mg/d) (n = 51) 2. Standard advice (n = 51) All subjects to drink six to eight glasses liquid and consume two servings dairy or 500 mg calcium carbonate daily.	American men (79%) and women (21%); mean age: 43 yr; exclusions: known metabolic conditions associated with nephrolithiasis, chronic small or large bowel disease	First nephrolithiasis episode (<1 yr before baseline); 0% with residual stone/fragments; stone ≥65% calcium oxalate
Kocvara et al [15]	242 (35)*	36	1. Tailored diet based on extensive metabolic evaluation [§] (113 completers) 2. General diet after limited metabolic evaluation (94 completers) 2. General diet after limited metabolic evaluation (94 completers)	Czech men (46%) and women (54%) of 207 completing trial; age range: 18–72 yr; exclusions: conditions associated with nephrolithiasis	First nephrolithiasis episode; 21% with residual stone/fragments; calcium stone
Borghi et al [13]	120 (17)	60	1. Low calcium diet (400 mg/d) (n = 60)	Italian men (100%) with idiopathic hypercalciuria; mean age: 45 yr; exclusions: conditions associated with calcium nephrolithiasis, previous visit to stone center,	Recurrent nephrolithiasis; 27% with residual stone/fragments; calcium oxalate stone

Study	No. of participants randomized, no. of withdrawals (n)	Duration, mo	1. Intervention regimen 2. Control regimen	Participant characteristics	Stone characteristics
			2. Normal-high calcium (1200 mg/d), low animal protein (<52 gm/d), low sodium (50 mmol/d) diet n = 60 Both groups to reduce oxalate and consume 2–3 l/d of water	current stone prevention treatment other than increased water intake	
Sarica et al [18]	45 (0)	24–36	1. High fluid intake (goal urine output >2.5 l/d) (n = 25) 2. No treatment (n = 20)	Turkish men (64%) and women (36%) who recently had completed shock wave lithotripsy for renal pelvis stone; mean age: 32 yr; exclusions: any metabolic abnormality	First nephrolithiasis episode; 53% with residual fragments; calcium oxalate stone
<i>Supplement studies</i>					
Pengamone et al [20]	48 (7)	18	1. <i>Orthosiphon grandiflorus</i> extract 2.5 gm twice daily (n = 24) 2. Sodium potassium citrate 5–10 gm after each meal (n = 24)	Thai men (48%) and women (52%); age range: 20–60 yr; exclusions: heart disease	First vs recurrent not stated; 100% with residual stone/fragments (>10 mm diameter at baseline), stone type not specified
Nishiura et al [19]	69 (0)	3	1. <i>Phyllanthus niruri</i> extract 450 mg three times daily (n = 33) 2. Placebo (<i>Chicorium sativum</i> extract) n = 36	Brazilian men (57%) and women (43%); mean age: 38 yr; exclusions: conditions associated with secondary calcium nephrolithiasis	First vs recurrent not stated; 100% with residual stone/fragments; calcium stone

* Number randomized to each treatment arm was not reported.

§ Among participants randomized to extensive metabolic evaluation, those identified with hypercalciuria were prescribed a diet including low animal protein and 750–1000 mg/d calcium; those identified with hyperuricosuria or hyperuricemia were prescribed a diet including low animal protein (80 gm/d meat products and 1–2 meatless days per week) and low purine; those identified with hyperoxaluria were prescribed a diet including low oxalate, regular intake of dairy products, and increased lemons and fiber; those identified with magnesium deficiency were prescribed a diet including increased fiber, regular intake of dairy products, and magnesium-containing mineral water; and those identified with hypocalciuria were prescribed a diet including low animal protein, one to two daily servings of lemons or orange juice, and increased fruit and vegetables.

Among participants randomized to a limited metabolic evaluation, general diet recommendations included 750–1000 mg/d of calcium, 100–120 gm/d of animal protein, oxalate restriction, increased fiber intake, and “moderate” sodium intake.

Table 3

Stone recurrence outcomes

Study	Definition of stone recurrence	Treatment groups	Stone recurrence, % (n/N)	p value
Dietary studies				
Shuster et al [17]	Symptomatic: self-report of physician; confirmed renal colic	Avoid soft drinks	33.7% (170/504)	0.023
		No intervention	40.6% (205/505)	
Borghi et al [13]	Composite: passage of new stone or renal colic; radiologically detected new stone (annual x-ray plus ultrasound)	High water intake	12.1% (12/99)	0.008
		No treatment	27.0% (27/100)	
Hiatt et al [16]	Composite: passage or surgical removal of new stone; radiologically detected new stone (annual x-ray)	Low animal protein; low purine; high fruit, whole grains and fiber; two dairy servings per day; high liquid intake	30.0% (12/40)	0.004
		Two dairy servings per day; high liquid intake	4.1% (2/49)	
Kocvara et al [15]	Composite: passage of new symptomatic stone (no details provided); radiologically detected new stone (x-ray and ultrasound; imaging interval not specified)	Extensive metabolic evaluation, tailored diet	6.2% (7/113)	<0.01
		Limited metabolic evaluation, general diet recommendations	19.1% (18/94)	
Borghi et al [14]	Composite: passage or surgical removal of new stone; renal colic or hematuria, with radiologically confirmed new stone; radiologically detected new stone (annual x-ray plus ultrasound)	Low calcium diet; high water intake, low oxalate	38.3% (23/60)	0.03
		Low animal protein, low sodium, higher calcium diet; high water intake, low oxalate	20.0% (12/60)	
Sarica et al [18]	Radiologic: detection by x-ray plus ultrasound (every 3 mo for 1 yr, every 6 mo for 1 yr, then annually)	High fluid intake	8.3% (1/12)*	<0.05
		No treatment	55.6% (5/9)	
Supplement studies				
Premgamone et al [20]	Radiologic: Percentage reduction in stone diameter per year (ultrasound every 5–7 wk)	Sodium potassium citrate	38.5% reduction per year at 18 mo	NS
		Orthosiphon grandiflorus	40.9% reduction per year at 18 mo	
Nishiura et al [19]	Symptomatic: passage of stone Radiologic: detection by ultrasound at end of study	Phyllanthus niruri	12.1% (4/33)	NS
		Placebo	13.9% (5/36)	

NS = not significant.

* Results in the table are shown for participants who were stone free at baseline. Among participants with retained stone fragments at baseline, 46.2% (6/13) of those randomized to high fluid intake versus 18.2% (2/11) of those allocated to no treatment were stone free at end of treatment ($p < 0.05$).