

Prevention of recurrent calcium nephrolithiasis

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GUIDELINES

- a. Patients with calcium lithiasis should be advised to consume a diet with a normal calcium intake (1000–1200 mg/day) with a fluid intake sufficient to result in the passage of 2 L of urine daily to reduce the risk of subsequent calcium stones. (Level II evidence)
- b. Thiazide and thiazide-like diuretics should be considered for patients with recurrent calcium lithiasis, particularly if associated with hypercalciuria. (Level I evidence)
- c. Oral citrate therapy should be considered for patients with recurrent calcium lithiasis particularly if associated with low urinary citrate excretion. (Level II evidence)
- d. Allopurinol should be considered for patients with recurrent calcium lithiasis in association with elevated serum uric acid or uricosuria. (Level II evidence)

BACKGROUND

Calcium-containing renal calculi are the most common stone type in reported series and recur in 26–53% of patients over a 10 year period.^{1–3} Because of this tendency, interventions aimed at reducing or preventing recurrence are an important strategy for reducing the morbidity associated with stone disease.

This guideline uses an evidence-based review of the published literature with the purpose of examining current interventions aimed at reducing the recurrence of calcium stones. The approach to this and the other related CARI guidelines is to score interventions on the quality of the evidence available. Formal guidelines are made when Level I or II evidence is available (i.e. randomized controlled trial (RCT) or meta-analysis). It is appreciated that not all interventions used for stone prevention may be adequately represented by this approach. Part of the function of this review is therefore to highlight where the available evidence for treatment of this condition can be improved.

Similarly, detailed discussion of the different metabolic abnormalities seen in patients with recurrent calcium stones is beyond the scope of this review. Where applicable, however, the role of different interventions in the presence of different metabolic abnormalities is discussed. Evidence based recommendations for the interventions considered in this review were only made where data available for their effect on stone recurrence. Recommendations were not made when the effect of an intervention on surrogate markers of stone risk (e.g. urinary parameters) was reported.

Level I or II evidence is available for the five different therapy groups considered below. Some but not all of these

interventions are additionally supported by evidence linking their mechanism of action with modifiable risk factors for stone recurrence.

SEARCH STRATEGY

Databases searched: Medline (1966 to June Week 3, 2004). MeSH terms and text words for kidney stones were combined with MeSH terms and text words for the interventions. The results were then combined with the Cochrane highly sensitive search strategy for RCTs and MeSH terms and text words for identifying meta-analyses and systematic reviews. The Cochrane Renal Group Specialized Register of RCTs was also searched for relevant trials not indexed in Medline.

Date of search: 29 June 2004.

WHAT IS THE EVIDENCE?

For the interventions examined, Level I or II evidence was available for most interventions in current clinical practice. The strongest evidence available was that for thiazide and thiazide-like diuretics. The applicability of this evidence is varied owing to the fact that different trials used these interventions in either a 'selected' (based, for example, on the presence of hypercalciuria) or 'unselected' manner. Furthermore, relegating a patient to lifelong therapy guided by these recommendations (with the associated risk of side-effects) needs to take into account the severity of the stone disease in that patient.

Modification of dietary constituents and fluid intake

The ideal study design to identify potential modifiable dietary risk factors for stone recurrence is a prospective cohort study. Several cohort studies have examined risk

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factors associated with either de novo or recurrent calcium lithiasis. The largest study, a prospective cohort study of more than 45 000 men, examined potential dietary risk factors for de novo calcium stone formation.⁵ Stone formation was more common in patients with a low fluid intake, a high animal protein intake and perhaps most surprisingly, those with a low dietary calcium (which was the strongest predictor in a multivariate analysis). Stone risk was inversely related to dietary potassium and magnesium intake was not independently associated with an increased risk of stone formation.⁵ A smaller cohort study of 522 patients examined risk factors associated with recurrence of calcium stones.⁶ In this latter study, patients who developed stone recurrence during follow-up had a significantly lower urine volume and a higher urine calcium excretion. Similarly, Tiselius and Sandvall⁷ reported a higher risk of recurrence for patients with renal calculi who had elevated levels of calcium oxalate supersaturation in their urine.

Case-control studies also give useful information on potential risk factors for stone recurrence. Several of these studies have compared dietary and biochemical parameters between patients with stone disease and matched controls. Not surprisingly, low urine volume was found to be more common in calcium stone patients in two of these studies^{8,9} and higher levels of urinary calcium excretion were more common in three further studies.⁹⁻¹¹ The role of dietary intake was examined in two further case-control studies. In keeping with the large cohort study reported previously, two studies found a lower level of dietary calcium intake in patients with calcium lithiasis when compared with controls.^{11,12} The case-control study of Al Zahrani *et al.*¹² also found statistically greater dietary intake of calories, sodium and carbohydrates in stone formers compared with controls.

Three randomized trials were identified which examined the effect of dietary modification on stone recurrence (Tables A1-A3). Increasing dietary fluid intake was examined in a RCT of 199 patients⁸ following their first stone episode. Patients in the intervention group were advised to increase their fluid intake to a level such that their urine volume exceeded 2 L/day. This intervention alone led to a 55% reduction in the risk of stone recurrence over 5 years of follow-up. Because the chance of adverse consequences from this recommendation is small, advice on increasing dietary fluid intake should be given to all patients with calcium stones.

Dietary intake of animal protein is another potential risk factor for stone recurrence identified in the large cohort study discussed before.⁴ Restricting dietary animal protein has been examined in two RCTs. In the RCT performed by Hiatt *et al.*,¹⁴ the risk of stone recurrence in 99 patients with de novo calcium stones was compared between those prescribed a low animal protein, normal calcium diet and those given a normal calcium diet. Advice on increased fluid intake was given to both groups. In this study, there was a nearly sixfold higher rate of calcium stone recurrence in the group randomized to the low protein diet. The effect of dietary modification of protein, calcium and sodium was examined in the RCT of Borghi *et al.*¹³ that included 120 patients. This trial compared the effect of two different diets

(a low calcium diet vs a normal calcium, low animal protein, low sodium diet) on the rate of stone recurrence in patients diagnosed with idiopathic hypercalciuria. Interestingly, there was no control group in this study and it is therefore unclear whether the reported result (i.e. a lower rate of stone recurrence in patients randomized to the low animal protein, normal calcium diet) represents an effect attributable to the protein or calcium levels of the diets.

In summary, the available Level II evidence supports the use of a diet with a 'normal' intake of calcium and with a fluid intake sufficient to increase the urinary volume to at least 2 L daily. There is insufficient evidence to recommend a either low animal protein or low calcium diet in calcium stone patients. No Level I or II evidence for other dietary manipulations was identified.

Thiazide and thiazide-like diuretics

As detailed previously, elevated urine calcium excretion is more common in patients with calcium stones.⁹⁻¹¹ Reducing urine calcium excretion with thiazide diuretics is therefore another potential method for reducing the risk of calcium stone recurrence. Literature review identified one meta-analysis and eight randomized studies of varying quality that examined thiazide and thiazide-like diuretics as a method for reducing calcium stone recurrence (Tables A4-A6). It should be emphasized that all of these studies only included patients with a proven history of stone recurrence (and not those with a single symptomatic stone).

In the meta-analysis reported by Pearle *et al.*,²¹ there was a 60% reduction (relative risk (RR) 0.4, 95% confidence interval (CI): 0.28, 0.56) in the risk of stone recurrence with the use of thiazide and thiazide-like diuretics. This meta-analysis included 459 patients from seven separate trials. The major limitation in the quality of this meta-analysis was the small number of included trials and the fact that the study population was not homogeneous (some trials included all calcium stone patients whereas others were limited to those with hypercalciuria).

Eight randomized trials of varying quality examining the effect of thiazide and thiazide-like diuretics were identified. As mentioned before, the inclusion criteria for these trials differed as to whether they included all calcium stone patients or only those proven to have hypercalciuria. Two trials examined patients with calcium lithiasis and hypercalciuria.^{15,20} In the largest of these studies involving 175 patients,²⁰ trichlormethiazide treatment resulted in a 70% reduction (RR 0.3, 95% CI: 0.17, 0.55) in the risk of stone formation in addition to advice on increased dietary intake of fluid. A smaller trial of 50 patients with hypercalciuria using the thiazide-like diuretic indapamide¹⁵ was inconclusive with a 20% loss to follow-up and a RR that failed to reach statistical significance (RR 0.4, 95% CI: 0.12, 1.2).

Six trials examined thiazide diuretics in unselected patients with calcium lithiasis.^{16-19,22,23} Significantly lower rates of stone recurrence were only found in one of these trials¹⁷ which randomized 83 patients with recurrent calcium oxalate stones to treatment with chlorthalidone.

In summary, it appears that thiazide diuretics have a role in the prevention of further calcium stones in patients with proven stone recurrence. The risk of potential side-effects with long-term thiazide treatment should be balanced against the severity of stone disease in individual patients.

Alkali citrate therapy

Through its effects on calcium solubility, urinary pH and stone nucleation, oral citrate is another potential intervention that may reduce the recurrence of calcium stones.^{24,25} Four randomized trials examining the use of oral citrate for the prevention of calcium stones were identified (Tables A7–A9). These studies differed in their inclusion criteria, with one trial specifying the presence of low urinary citrate before inclusion.²⁶ All trials were small in size (50–64 patients) and of varying quality. Oral citrate was given in three divided doses either as the potassium or as magnesium salt. Theoretical support for the use of potassium and magnesium salts in these trials comes from the observation that dietary intake of potassium and magnesium were both inversely related to the risk of *de novo* calcium stone formation in the cohort study mentioned above.⁵

Three of the four trials showed a significant reduction in stone recurrence when citrate therapy was combined with advice on increasing dietary fluid.^{26,27,29} The size of this reduction varied from 65% to 100%. No recurrence was seen in the intervention group in one trial.²⁹

A potential barrier to the widespread use of citrate is the relatively high rate of discontinuation of citrate therapy due to adverse effects (including nausea, diarrhoea, bloating and rash). In the reported trials, the frequency of discontinuation of citrate treatment due to adverse effects ranged from 10% to 25%; however, an even greater proportion of patients who remained compliant with therapy developed these symptoms.²⁷

In summary, citrate therapy has been proven to be effective at preventing further stone formation in patients with recurrent calcium stones. The frequency of side-effects associated with citrate and the need for long-term treatment is likely to limit the population of patients eligible for this treatment.

Allopurinol

Increased excretion of uric acid in the urine may have a role in promoting the growth of calcium stones.³⁰ Four trials examining allopurinol therapy in the prevention of recurrent calcium oxalate stones were identified (Tables A10–A12).

Two of these trials examined the use of allopurinol in calcium stone patients who were found to have either hyperuricaemia³² or hyperuricosuria.³¹ In the study of Smith,³² 92 patients with recurrent calcium stones and hyperuricaemia were randomized to treatment with placebo or a combination of allopurinol and alkalinization of the urine with oral bicarbonate. Patients were followed up for up to 5 years; however, suitable data for calculation of the RR were only available at 12 months. Patients randomized

to allopurinol and bicarbonate had a 60% reduction in the risk of stones at 12 months, in this study.

The study of Ettinger *et al.*³¹ reported the results for 60 patients with recurrent calcium stones and hyperuricosuria randomized to treatment with placebo or allopurinol. Patients with hypercalciuria were excluded. This trial reported a 47% reduction in stone recurrence at 24 months of follow-up.

An additional RCT randomized an unselected group of patients with recurrent calcium lithiasis to treatment with allopurinol.²³ Only 17 of these patients were randomized to allopurinol (separate intervention arms were randomized to phosphate and magnesium) and no placebo was used in the control arm. The RR of stone recurrence in this study was not significantly different between the control and intervention groups.

The fourth RCT comprised the second intervention arm of a study wherein patients with recurrent calcium lithiasis were randomized to treatment with placebo or a combination of indapamide and allopurinol.¹⁵ No significant difference in stone recurrence was seen in the intervention group in this study.

In summary, there is Level II evidence to support the use of allopurinol for the prevention of recurrent calcium lithiasis in the presence of either hyperuricaemia or hyperuricosuria.

Oral magnesium and phosphate therapy

The rationale for the use of magnesium therapy for the prevention of calcium lithiasis is on the basis of *in vitro* data showing that magnesium can inhibit the formation of calcium oxalate crystals as well as several uncontrolled trials that have reported its benefits.³³ The level of dietary magnesium was also inversely associated with the risk of *de novo* stone formation in the large cohort study already mentioned:⁵ Phosphate therapy has also been recommended as it reduces vitamin D levels leading to a reduction in urine calcium excretion.³⁴ Two RCTs have examined the efficacy of either magnesium or phosphate for stone prevention (Tables A12–A15).

In the study of Ettinger *et al.*,¹⁷ the risk of stone recurrence was compared between 84 patients randomized to placebo or oral magnesium hydroxide. A separate intervention arm in this study examined the effect of chlorthalidone and has been considered separately before. The risk of stone recurrence was not different between the placebo and magnesium hydroxide arms. A separate small study of 54 patients compared the risk of stone recurrence between patients randomized to treatment with either magnesium hydroxide or oral phosphate.²³ This study included two additional allopurinol and thiazide intervention arms and did not use a placebo in the control group. No significant difference in the risk of stone recurrence was found in either the magnesium or phosphate treatment groups.

In summary, although the size and number of available trials was small, it appears unlikely that either oral magnesium or phosphate therapy is beneficial in the prevention of calcium stone recurrence.

SUMMARY OF THE EVIDENCE

See enclosed evidence (Tables A1–A15) in the Appendices.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Association of Urology: Guidelines not graded on strength of evidence.

- **Calcium stones and hypercalciuria:** Thiazides and/or alkaline citrate;
- **Calcium stones and hyperoxaluria:** Alkaline citrate;
- **Calcium stones and hyperuricosuria:** Allopurinol.

INTERNATIONAL GUIDELINES

American Academy of Family Physicians: No recommendation.

American Urological Association: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

1 Run a randomized trial to examine dietary sodium and caloric restriction as an intervention to prevent calcium stone recurrence.

2 Run a randomized trial to compare the effect of a low protein, normal calcium diet with a normal calcium diet alone, on calcium stone recurrence.

CONFLICT OF INTEREST

Lukas Kairaitis has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDICES

Table A1 Characteristics of included dietary and fluid modification studies

Study ID (author, year)	n	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow-up (months)	Comments
Borghi <i>et al.</i> , 2002 ¹³	120	Randomized trial (no control group)	Italian University Hospital	Men with recurrent calcium oxalate lithiasis and idiopathic hypercalciuria	Low animal protein, low salt, normal calcium diet	Low calcium diet	60	No placebo arm, advice on increased fluid intake in all groups
Borghi <i>et al.</i> , 1996 ⁸	199	Randomized controlled clinical trial	Italian University Hospital	Adults with calcium lithiasis	Increased dietary fluid intake	No treatment	60	
Hiatt <i>et al.</i> , 1996 ¹⁴	99	Randomized controlled clinical trial	Patients from a Californian HMO database	Adults aged 20–60 years with a single proven calcium oxalate stone	Low animal protein diet and increased dietary fluid intake	Increased dietary fluid intake only	6–50	Patients with RTA and hyperparathyroidism excluded

HMO, Health Maintenance Organisation; RTA, renal tubular acidosis.

Table A2 Quality of included dietary and fluid modification studies

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow-up (%)
		Participants	Investigators	Outcome assessors		
Borghi <i>et al.</i> , 2002 ¹³	Sequentially labelled, opaque, sealed envelopes	No	Yes	Yes	Yes	14.0
Borghi <i>et al.</i> , 1996 ⁸	Not specified	No	Not specified	Not specified	Yes	10.0
Hiatt <i>et al.</i> , 1996 ¹⁴	Not specified	No	Yes	Yes	Yes	21.0

Table A3 Results of included dietary and fluid modification studies

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (95% CI)	Risk difference (95% CI)
Borghi <i>et al.</i> , 2002 ¹³	New calculous event	12/60 (low animal protein, normal calcium diet)	23/60 (low calcium diet)	0.52 (0.29, 0.95)	–0.18 (–0.34, –0.02)
Borghi <i>et al.</i> , 1996 ⁸	New calculous event	12/99	27/100	0.45 (0.24, 0.84)	–0.15 (–0.26, –0.04)
Hiatt <i>et al.</i> , 1996 ¹⁴	New calculous event	12/50	2/49	5.9 (1.4, 25.0)	0.20 (0.07, 0.33)

Table A4 Description of included thiazide studies

Study ID (author, year)	n	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow-up (months)	Comments
Borghi <i>et al.</i> , 1993 ¹⁵	50	RCT	University Hospital Clinic	Patients with recurrent calcium lithiasis and hypercalciuria	Indapamide 2.5 mg daily and dietary/fluid advice	Dietary advice and increased fluid intake	36	A third group of 21 patients treated with indapamide and allopurinol
Brooks <i>et al.</i> , 1981 ¹⁶	62	RCT	University Hospital Clinic	Adults with recurrent calcium stones	Bendroflumethiazide 2.5 mg three times daily	Placebo	12-48	
Erttinger <i>et al.</i> , 1988 ¹⁷	83	RCT	Patients from a Californian HMO database	Adults with recurrent calcium oxalate stones	Chlorthalidone (25/50 mg) and dietary/fluid advice	Placebo and dietary/fluid advice	36	A third group of 51 patients treated with oral MgOH
Fernandez-Rodriguez <i>et al.</i> , 2001 ¹⁸	150	RCT	Spanish Hospital	Adults with recurrent calcium lithiasis	1.50 mg hydrochlorothiazide and dietary/fluid advice 2.50 mg hydrochlorothiazide, 20 mEq potassium citrate and dietary/fluid advice 25 mg hydrochlorothiazide and 600 mg KCl daily	Dietary/fluid advice only	36	
Laerum & Larsen, 1984 ¹⁹	50	RCT	Norwegian general practice	Patients with recurrent calcium lithiasis	Trichlormethiazide 4 mg daily	Dietary advice and increased fluid intake	12-51	Dietary advice and increased fluid intake in all groups
Ohkawa <i>et al.</i> , 1992 ²⁰	175	RCT	University Hospitals	Adults with calcium lithiasis and hypercalciuria	Thiazides or thiazide-like diuretics	Dietary and fluid advice only	6-5.7 years	Dietary advice and increased fluid intake in all groups
Pearle <i>et al.</i> , 1999 ²¹	459	Meta-analysis of RCTs	Not specified	Adults with recurrent calcium lithiasis without hyperparathyroidism	Hydrochlorothiazide 25 mg twice daily	Placebo or conservative management	12-48	
Scholz <i>et al.</i> , 1982 ²²	51	RCT	Not specified	Adults with recurrent calcium lithiasis	100 mg hydrochlorothiazide daily and dietary/fluid advice	Placebo	12	Three additional intervention groups treated with MgOH, phosphate and allopurinol
Wilson <i>et al.</i> , 1984 ²³	44	RCT	Canadian University Hospital	Adults with recurrent calcium lithiasis				

HMO, Health Maintenance Organisation; RCT, randomized controlled trial.

Table A5 Quality of included thiazide studies

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to- treat analysis	Loss to follow-up (%)
		Participants	Investigators	Outcome assessors		
Borghi <i>et al.</i> , 1993 ¹⁵	Not specified	No	No	No	Yes	20%
Brocks <i>et al.</i> , 1981 ¹⁶	Not specified	Yes	Yes	Not specified	Unclear	Not given
Ettinger <i>et al.</i> , 1988 ¹⁷	Not specified	Yes	Not specified	Yes	No	Not specified
Fernandez-Rodriguez <i>et al.</i> , 2001 ¹⁸	Not specified	No	Not specified	Not specified	Yes	None, dose of HCTZ reduced to 25 mg in 17% of patients due to adverse effects
Laerum & Larsen, 1984 ¹⁹	Not specified	Yes	Yes	Yes	Yes	4%
Ohkawa <i>et al.</i> , 1992 ²⁰	Not specified	No	No	No	No	16% excluded or withdrew
Scholz <i>et al.</i> , 1982 ²²	Not specified	Yes	Yes	Not specified	No	Not given
Wilson <i>et al.</i> , 1984 ²³	Not specified	No	No	No	No	16%

HCTZ, hydrochlorthiazide.

Table A6 Results of included thiazide studies

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk	Risk difference
				(95% CI)	(95% CI)
Borghi <i>et al.</i> , 1993 ¹⁵	New calculous event	3/19 (indapamide) 4/21 (indapamide + allopurinol)	9/21 (placebo)	0.37 (indapamide)	-0.27
				(0.12, 1.2)	(-0.54, 0.00)
Brocks <i>et al.</i> , 1981 ¹⁶	New calculous event	5/33	5/29	0.44 (indapamide + allopurinol)	-0.24
				(0.16, 1.2)	(-0.51, 0.03)
Ettinger <i>et al.</i> , 1988 ¹⁷	New calculous event	6/52 (chlorthalidone arm)	14/31 (placebo)	0.88	-0.02
				(0.3, 2.7)	(-0.20, 0.16)
Fernandez- Rodriguez <i>et al.</i> , 2001 ¹⁸	New calculous event	11/50 (thiazide group) 10/50 (thiazide + citrate group)	20/50	0.26 (chlorthalidone vs placebo)	-0.34
				(0.11, 0.60)	(-0.53, -0.14)
Laerum &Larsen, 1984 ¹⁹	New calculous event	5/23	12/25	0.55 (thiazide group)	-0.08
				(0.30, 1.02)	(-0.36, 0.00)
Ohkawa <i>et al.</i> , 1992 ²⁰	New calculous event	11/82	41/93	0.5 (thiazide + citrate)	-0.20
				(0.26, 0.96)	(0.38, -0.02)
Pearle <i>et al.</i> , 1999 ²¹	Meta-analysis of thiazide and indapamide trials	36/234	87/225	0.45	-0.26
				(0.19, 1.1)	(-0.52, 0.00)
Scholz <i>et al.</i> , 1982 ²²	Stone passage within observation period	6/25	6/26	0.30	-0.31
				(0.17, 0.55)	(-0.43, -0.18)
Wilson <i>et al.</i> , 1984 ²³	Stone recurrence in follow-up	7/23 (thiazide group)	8/21	0.40	-0.23
				(0.28, 0.56)	(-0.31, -0.15)
Wilson <i>et al.</i> , 1984 ²³	Stone recurrence in follow-up	7/23 (thiazide group)	8/21	1.04	0.01
				(0.39, 2.8)	(-0.22, 0.24)
Wilson <i>et al.</i> , 1984 ²³	Stone recurrence in follow-up	7/23 (thiazide group)	8/21	0.8	-0.08
				(0.35, 1.8)	(-0.36, 0.20)

Table A7 Description of included citrate studies

Study ID (author, year)	n	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow- up (months)	Comments
Barcelo <i>et al.</i> , 1993 ²⁶	57	RCT	Spanish Hospital Urology Department	Adults with recurrent calcium stones and hypocitraturia	Oral potassium citrate 20 mEq tds and dietary and fluid advice	Placebo and dietary and fluid advice	36	Patients with hypercalciuria, hyperuricosuria and hyperoxaluria excluded
Ettinger <i>et al.</i> , 1997 ²⁷	64	RCT	Patients from a Californian HMO database	Adults with recurrent calcium oxalate stones	Oral potassium magnesium citrate tds and dietary and fluid advice	Placebo and dietary and fluid advice	36	Patients with RTA excluded
Hofbauer <i>et al.</i> , 1994 ²⁸	50	RCT	Austrian University Hospital	Adults with recurrent 'idiopathic' calcium oxalate stones	Oral sodium potassium citrate titrated to urine pH of 7.1–7.2 + dietary and fluid advice	Dietary and fluid advice alone	36	Primary hyperparathyroidism, hypercalcaemia and RTA excluded
Soygur <i>et al.</i> , 2002 ²⁹	56	RCT (no placebo group)	Turkish University Hospital	Adults stone- free after treatment of calcium oxalate stones with ESWL	Potassium citrate 60 mEq daily	No treatment	12	Dietary advice and increased fluid intake in all groups

ESWL, extracorporeal shock wave lithotripsy; HMO, Health Maintenance Organisation; RCT, randomized controlled trial; RTA, renal tubular acidosis.

Table A8 Quality of included citrate studies

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to- treat analysis	Loss to follow-up (%)
		Participants	Investigators	Outcome assessors		
Barcelo <i>et al.</i> , 1993 ²⁶	Not specified	Yes	Yes	Not specified	No	21
Ettinger <i>et al.</i> , 1997 ²⁷	Not specified	Yes	Yes	Yes	Yes	36
Hofbauer <i>et al.</i> , 1994 ²⁸	Not specified	No	No	No	No	24
Soygur <i>et al.</i> , 2002 ²⁹	Not specified	No	Yes	Yes	No	18

Table A9 Results of included citrate studies

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (95% CI)	Risk difference (95% CI)
Barcelo <i>et al.</i> , 1993 ²⁶	New calculous event	5/18	16/20	0.35 (0.16, 0.75)	-0.52 (-0.79, -0.25)
Ettinger <i>et al.</i> , 1997 ²⁷	New calculous event	4/31	21/33	0.20 (0.08, 0.52)	-0.51 (-0.71, -0.31)
Hofbauer <i>et al.</i> , 1994 ²⁸	New calculous event	11/16	16/22	0.94 (0.65, 1.23)	-0.04 (-0.33, 0.25)
Soygur <i>et al.</i> , 2002 ²⁹	New calculous event	0/28	8/28	0 (0, 0)	-0.29 (-0.46, -0.11)

Table A10 Description of included allopurinol studies

Study ID (author, year)	n	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow -up (months)	Comments
Borghi <i>et al.</i> , 1993 ¹⁵	42	RCT	University Hospital Clinic	Patients with recurrent calcium lithiasis and hypercalciuria	Allopurinol 300 mg + Indapamide 2.5 mg daily plus dietary advice and increased fluid intake	Dietary advice and increased fluid intake	36	A third group of 19 patients treated with indapamide alone
Ettinger <i>et al.</i> , 1986 ³¹	60	RCT	Patients from a Californian HMO database	Adults with recurrent calcium oxalate stones, hyperuricosuria and normocalciuria	Oral allopurinol 100 mg tds plus dietary/ fluid advice	Placebo and dietary/fluid advice	24	
Smith, 1977 ³²	92	RCT	University Hospital Urology Department	Adults with recurrent calcium oxalate stones and elevated serum uric acid	Oral allopurinol 100 mg tds and urinary alkalinization with oral bicarbonate	Placebo and urinary alkalinization with oral bicarbonate	12	Patients who withdrew before 6 months excluded
Wilson <i>et al.</i> , 1984 ²³	38	RCT	Canadian University Hospital	Adults with recurrent calcium lithiasis	Allopurinol 300 mg daily plus dietary advice and increased fluid intake	Diet and increased fluid intake only	12–36	3 additional intervention arms treated with thiazides, MgOH or phosphate

RCT, randomized controlled trial.

Table A11 Quality of included allopurinol studies

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow-up (%)
		Participants	Investigators	Outcome assessors		
Borghi <i>et al.</i> , 1993 ¹⁵	Not specified	No	No	No	Yes	20.0
Ettinger <i>et al.</i> , 1986 ³¹	Not specified	Yes	Yes	Yes	No	17.0
Smith, 1977 ³²	Third party	Yes	No	No	Yes	30.0
Wilson <i>et al.</i> , 1984 ²³	Not specified	No	No	No	No	16.0

Table A12 Results of included allopurinol studies

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (95% CI)	Risk difference (95% CI)
Borghi <i>et al.</i> , 1993 ¹⁵	New calculous event	4/21 (indapamide + allopurinol)	9/21 (placebo)	0.44 (0.16, 1.2)	-0.24 (-0.51, 0.03)
Ettinger <i>et al.</i> , 1986 ³¹	New calculous event	9/29	18/31	0.53 (0.29, 0.99)	-0.27 (-0.51, -0.03)
Smith, 1977 ³²	New stone	17/44	36/39	0.42 (0.29, 0.61)	-0.54 (-0.70, -0.37)
Wilson <i>et al.</i> , 1984 ²³	Stone recurrence in follow-up	8/17 (allopurinol group)	8/21	1.2 (0.6, 2.6)	0.09 (-0.23, 0.40)

Table A13 Description of included studies of magnesium/phosphate treatment

Study ID (author, year)	n	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow-up (months)	Comments
Ettinger <i>et al.</i> , 1988 ¹⁷	84	RCT	Patients from a Californian HMO database	Adults with recurrent calcium oxalate stones	Oral MgOH and dietary/ fluid advice	Placebo and dietary/fluid advice	36	A separate group of 52 patients were treated with chlorthalidone
Wilson <i>et al.</i> , 1984 ²³	54	RCT	Canadian University Hospital	Adults with recurrent calcium lithiasis	1.15 g sodium phosphate daily, 2.4 mg MgOH daily	Diet and increased fluid intake only	12–36	Two separate groups treated with thiazide or allopurinol in the same study

RCT, randomized controlled trial.

Table A14 Quality of included studies of magnesium/phosphate treatment

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow-up (%)
		Participants	Investigators	Outcome assessors		
Ettinger <i>et al.</i> , 1988 ¹⁷	Not specified	Yes	Not specified	Yes	No	Not specified
Wilson <i>et al.</i> , 1984 ²³	Not specified	No	No	No	No	16.0

Table A15 Results of included studies of magnesium/phosphate treatment

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (95% CI)	Risk difference (95% CI)
Ettinger <i>et al.</i> , 1988 ¹⁷	New calculous event (stone passage, radiological enlargement or new stone formation)	15/51 (MgOH arm)	14/31 (placebo)	0.65 (MgOH vs placebo) (0.37, 1.2)	-0.16 (-0.37, 0.06)
Wilson <i>et al.</i> , 1984 ²³	Stone recurrence in follow-up	6/17 (phosphate group) 7/16 (MgOH group)	8/21	0.93 (0.4, 2.2) 1.1 (0.5, 2.5)	-0.03 (-0.34, 0.28) 0.06 (-0.26, 0.38)