**NEPHROLOGY** 2007; **12**, S11–S20 doi:10.1111/j.1440-1797.2006.00723.x

# Prevention of recurrent calcium nephrolithiasis

Date written: May 2005
Final submission: July 2006
Author: Lukas Kairaitis



**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

Correspondence: Dr Lukas Kairaitis, Department of Renal Medicine, Westmead Hospital, Westmead NSW 2145, Australia. Email: lukask@med.usyd.edu.au

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 Sandvall[7] 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 patients[8] 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 indapamide[15] 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 trials[17] 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 hyperuricaemia[32] 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.

## REFERENCES


1. Ahlstrand C, Tiselius HG. Recurrences during a 10-year follow-up after first renal stone episode. *Urol. Res.* 1990; **18**: 397–9.
2. Ljunghall S, Danielson BG. A prospective study of renal stone recurrences. *Br. J. Urol.* 1984; **56**: 122–4.
3. Trinchieri A, Ostini F, Nespoli R *et al.* A prospective study of recurrence rate and risk factors for recurrence after a first renal stone. *J. Urol.* 1999; **162**: 27–30.
4. Curhan GC, Willett WC, Rimm EB *et al.* A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N. Engl. J. Med.* 1993; **328**: 833–8.
5. Taylor EN, Stampfer MS, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of followup. *J. Am. Soc. Nophrol.* 2004; **15**: 3225–32.
6. Strauss AL, Coe FL, Deutsch L *et al.* Factors that predict relapse of calcium nephrolithiasis during treatment: A prospective study. *Am. J. Med.* 1982; **72**: 17–24.
7. Tiselius HG, Sandvall K. How are urine composition and stone disease affected by therapeutic measures at an outpatient stone clinic? *Eur. Urol.* 1990; **17**: 206–12.
8. Borghi L, Meschi T, Amato F *et al.* Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: A 5-year randomized prospective study. *J. Urol.* 1996; **155**: 839–43.
9. Curhan GC, Willett WC, Speizer FE *et al.* Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. *Kidney Int.* 2001; **59**: 2290–98.
10. Cirillo M, Stellato D, Panarelli P *et al.* Cross-sectional and prospective data on urinary calcium and urinary stone disease. *Kidney Int.* 2003; **63**: 2200–206.
11. Leonetti F, Dussol B, Berthezene P *et al.* Dietary and urinary risk factors for stones in idiopathic calcium stone formers compared with healthy subjects. *Nephrol. Dial. Transplant.* 1998; **13**: 617–22.
12. Al Zahrani H, Norman RW, Thompson C *et al.* The dietary habits of idiopathic calcium stone-formers and normal control subjects. *BJU Int.* 2000; **85**: 616–20.
13. Borghi L, Schianchi T, Meschi T *et al.* Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N. Engl. J. Med.* 2002; **346**: 77–84.
14. Hiatt RA, Ettinger B, Caan B *et al.* Randomized controlled trial of a low animal protein, high fiber diet in the prevention of recurrent calcium oxalate kidney stones. *Am. J. Epidemiol.* 1996; **144**: 25–33.
15. Borghi L, Meschi T, Guerra A *et al.* Randomized prospective study of a nonthiazide diuretic, indapamide, in preventing calcium stone recurrences. *J. Cardiovasc. Pharmacol.* 1993; **22** (Suppl. 6): S78–86.
16. Brocks P, Dahl C, Wolf H *et al.* Do thiazides prevent recurrent idiopathic renal calcium stones? *Lancet* 1981; **2**: 124–5.
17. Ettinger B, Citron JT, Livermore B *et al.* Chlorthalidone reduces calcium oxalate calculous recurrence but magnesium hydroxide does not. *J. Urol.* 1988; **139**: 679–84.
18. Fernandez-Rodriguez A, Arrabal Martin M, Garcia Ruiz MJ *et al.* Effect of thiazide therapy in the prophylaxis of calcium lithiasis. *Arch. Esp. Urol.* 2001; **54**: 1047–54.
19. Laerum E, Larsen S. Thiazide prophylaxis of urolithiasis. A double-blind study in general practice. *Acta Med. Scand.* 1984; **215**: 383–9.
20. Ohkawa M, Tokunaga S, Nakashima T *et al.* Thiazide treatment for calcium urolithiasis in patients with idiopathic hypercalciuria. *Br. J. Urol.* 1992; **69**: 571–6.
21. Pearle MS, Roehrborn CG, Pak CY. Meta-analysis of randomized trials for medical prevention of calcium oxalate nephrolithiasis. *J. Endourol.* 1999; **13**: 679–85.
22. Scholz D, Schwille PO, Sigel A. Double-blind study with thiazide in recurrent calcium lithiasis. *J. Urol.* 1982; **128**: 903–7.
23. Wilson DR, Strauss AL, Manuel MA. Comparison of medical treatments for the prevention of recurrent calcium nephrolithiasis. *Urol. Res.* 1984; **12**: 39–40.
24. Meyer JL, Smith LH. Growth of calcium oxalate crystals. II. Inhibition by natural urinary crystal growth inhibitors. *Invest. Urol.* 1975; **13**: 36–9.
25. Pak CY. Citrate and renal calculi: An update. *Miner Electrolyte Metab.* 1994; **20**: 371–7.
26. Barcelo P, Wuhl O, Servitge E *et al.* Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J. Urol.* 1993; **150**: 1761–4.
27. Ettinger B, Pak CY, Citron JT *et al.* Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J. Urol.* 1997; **158**: 2069–73.
28. Hofbauer J, Hobarth K, Szabo N *et al.* Alkali citrate prophylaxis in idiopathic recurrent calcium oxalate urolithiasis – a prospective randomized study. *Br. J. Urol.* 1994; **73**: 362–5.
29. Soygur T, Akbay A, Kupeli S. Effect of potassium citrate therapy on stone recurrence and residual fragments after shockwave lithot-

ripsy in lower caliceal calcium oxalate urolithiasis: A randomized controlled trial. *J. Endourol.* 2002; **16**: 149–52.
30. Finlayson B, Newman RC, Hunter PT. The role of urate and allopurinol in stone disease: A review. In: Schwille PO, Smith LH, Robertson WG (eds). *Urolithiasis and Related Clinical Research*. New York: Plenum Press, 1985; 517–19.
31. Ettinger B, Tang A, Citron JT *et al.* Randomized trial of allopurinol in the prevention of calcium oxalate calculi. *N. Engl. J. Med.* 1986; **315**: 1386–9.
32. Smith MJ. Placebo versus allopurinol for renal calculi. *J. Urol.* 1977; **117**: 690–92.
33. Johansson G, Backman U, Danielson BG *et al.* Magnesium metabolism in renal stone formers. Effects of therapy with magnesium hydroxide. *Scand. J. Urol. Nephrol. Suppl.* 1980; **53**: 125–34.
34. Ettinger B. Recurrent nephrolithiasis: Natural history and effect of phosphate therapy. A double-blind controlled study. *Am. J. Med.* 1976; **61**: 200–206.

## 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 *et al.*, 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 *et al.*, 1996[8] | 199 | Randomized controlled clinical trial | Italian University Hospital | Adults with calcium lithiasis | Increased dietary fluid intake | No treatment | 60 | |
| Hiatt *et al.*, 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 *et al.*, 2002[13] | Sequentially labelled, opaque, sealed envelopes | No | Yes | Yes | Yes | 14.0 |
| Borghi *et al.*, 1996[8] | Not specified | No | Not specified | Not specified | Yes | 10.0 |
| Hiatt *et al.*, 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 *et al.*, 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 *et al.*, 1996[8] | New calculous event | 12/99 | 27/100 | 0.45 (0.24, 0.84) | –0.15 (–0.26, –0.04) |
| Hiatt *et al.*, 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 *et al.*, 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 |
| Brocks *et al.*, 1981[16] | 62 | RCT | University Hospital Clinic | Adults with recurrent calcium stones | Bendroflumethiazide 2.5 mg three times daily | Placebo | 12–48 | |
| Ettinger *et al.*, 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 *et al.*, 2001[18] | 150 | RCT | Spanish Hospital | Adults with recurrent calcium lithiasis | 1.50 mg hydrochlorothiazide and dietary/fluid advice<br>2.50 mg hydrochlorothiazide, 20 mEq potassium citrate and dietary/fluid advice | Dietary/fluid advice only | 36 | |
| Laerum & Larsen, 1984[19] | 50 | RCT | Norwegian general practice | Patients with recurrent calcium lithiasis | 25 mg hydrochlorothiazide and 600 mg KCl daily | Dietary advice and increased fluid intake | 12–51 | Dietary advice and increased fluid intake in all groups |
| Ohkawa *et al.*, 1992[20] | 175 | RCT | University Hospitals | Adults with calcium lithiasis and hypercalciuria | Trichlormethiazide 4 mg daily | Dietary and fluid advice only | 6–5.7 years | Dietary advice and increased fluid intake in all groups |
| Pearle *et al.*, 1999[21] | 459 | Meta-analysis of RCTs | | | Thiazides or thiazide-like diuretics | Placebo or conservative management | 12–48 | |
| Scholz *et al.*, 1982[22] | 51 | RCT | Not specified | Adults with recurrent calcium lithiasis without hyperparathyroidism | Hydrochlorothiazide 25 mg twice daily | Placebo | 12 | |
| Wilson *et al.*, 1984[23] | 44 | RCT | Canadian University Hospital | Adults with recurrent calcium lithiasis | 100 mg hydrochlorothiazide daily and dietary/fluid advice | Dietary advice and increased fluid intake only | 12–36 | Three additional intervention groups treated with MgOH, phosphate and allopurinol |

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 *et al.*, 1993[15] | Not specified | No | No | No | Yes | 20% |
| Brocks *et al.*, 1981[16] | Not specified | Yes | Yes | Not specified | Unclear | Not given |
| Ettinger *et al.*, 1988[17] | Not specified | Yes | Not specified | Yes | No | Not specified |
| Fernandez-Rodriguez *et al.*, 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 *et al.*, 1992[20] | Not specified | No | No | No | No | 16% excluded or withdrew |
| Scholz *et al.*, 1982[22] | Not specified | Yes | Yes | Not specified | No | Not given |
| Wilson *et al.*, 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 (95% CI) | Risk difference (95% CI) |
|---|---|---|---|---|---|
| Borghi *et al.*, 1993[15] | New calculous event | 3/19 (indapamide)<br>4/21 (indapamide + allopurinol) | 9/21 (placebo) | 0.37 (indapamide) (0.12, 1.2)<br>0.44 (indapamide + allopurinol) (0.16, 1.2) | –0.27 (–0.54, 0.00)<br>–0.24 (–0.51, 0.03) |
| Brocks *et al.*, 1981[16] | New calculous event | 5/33 | 5/29 | 0.88 (0.3, 2.7) | –0.02 (–0.20, 0.16) |
| Ettinger *et al.*, 1988[17] | New calculous event | 6/52 (chlorthalidone arm) | 14/31 (placebo) | 0.26 (chlorthalidone *vs* placebo) (0.11, 0.60) | –0.34 (–0.53, –0.14) |
| Fernandez-Rodriguez *et al.*, 2001[18] | New calculous event | 11/50 (thiazide group)<br>10/50 (thiazide + citrate group) | 20/50 | 0.55 (thiazide group) (0.30, 1.02)<br>0.5 (thiazide + citrate) (0.26, 0.96) | –0.08 (–0.36, 0.00)<br>–0.20 (0.38, –0.02) |
| Laerum &Larsen, 1984[19] | New calculous event | 5/23 | 12/25 | 0.45 (0.19, 1.1) | –0.26 (–0.52, 0.00) |
| Ohkawa *et al.*, 1992[20] | New calculous event | 11/82 | 41/93 | 0.30 (0.17, 0.55) | –0.31 (–0.43, –0.18) |
| Pearle *et al.*, 1999[21] | Meta-analysis of thiazide and indapamide trials | 36/234 | 87/225 | 0.40 (0.28, 0.56) | –0.23 (–0.31, –0.15) |
| Scholz *et al.*, 1982[22] | Stone passage within observation period | 6/25 | 6/26 | 1.04 (0.39, 2.8) | 0.01 (–0.22, 0.24) |
| Wilson *et al.*, 1984[23] | Stone recurrence in follow-up | 7/23 (thiazide group) | 8/21 | 0.8 (0.35, 1.8) | –0.08 (–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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 1993[26] | Not specified | Yes | Yes | Not specified | No | 21 |
| Ettinger *et al.*, 1997[27] | Not specified | Yes | Yes | Yes | Yes | 36 |
| Hofbauer *et al.*, 1994[28] | Not specified | No | No | No | No | 24 |
| Soygur *et al.*, 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 *et al.*, 1993[26] | New calculous event | 5/18 | 16/20 | 0.35 (0.16, 0.75) | –0.52 (–0.79, –0.25) |
| Ettinger *et al.*, 1997[27] | New calculous event | 4/31 | 21/33 | 0.20 (0.08, 0.52) | –0.51 (–0.71, –0.31) |
| Hofbauer *et al.*, 1994[28] | New calculous event | 11/16 | 16/22 | 0.94 (0.65, 1.23) | –0.04 (–0.33, 0.25) |
| Soygur *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 1993[15] | Not specified | No | No | No | Yes | 20.0 |
| Ettinger *et al.*, 1986[31] | Not specified | Yes | Yes | Yes | No | 17.0 |
| Smith, 1977[32] | Third party | Yes | No | No | Yes | 30.0 |
| Wilson *et al.*, 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 *et al.*, 1993[15] | New calculous event | 4/21(indapamide + allopurinol) | 9/21 (placebo) | 0.44 (indapamide + allopurinol) (0.16, 1.2) | –0.24 (–0.51, 0.03) |
| Ettinger *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 1988[17] | Not specified | Yes | Not specified | Yes | No | Not specified |
| Wilson *et al.*, 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 *et al.*, 1988[17] | New calculous event (stone passage, radiological enlargement or new stone formation) | 15/31 (MgOH arm) | 14/31 (placebo) | 0.65 (MgOH *vs* placebo) (0.37, 1.2) | –0.16 (–0.37, 0.06) |
| Wilson *et al.*, 1984[23] | Stone recurrence in follow-up | 6/17 (phosphate group)<br>7/16 (MgOH group) | 8/21 | 0.93 (0.4, 2.2)<br>1.1 (0.5, 2.5) | –0.03 (–034, 0.28)<br>0.06 (–0.26, 0.38) |