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[Intervention Review]

Pharmacological interventions for preventing complications in idiopathic hypercalciuria

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ABSTRACT

Background

Idiopathic hypercalciuria is an inherited metabolic abnormality characterised by excessive amounts of calcium excreted into the urine in patients with normal serum levels of calcium. The morbidity of hypercalciuria is related to kidney stone disease and bone demineralization. In children, hypercalciuria can cause recurrent haematuria, frequency-dysuria syndrome, urinary tract infection and abdominal and lumbar pain. Several pharmacological treatments have been described that can decrease the levels of urinary calcium or its index of urinary crystallization.

Objectives

To assess the benefits and harms of pharmacological interventions for preventing complications and decreasing urological symptoms in patients with idiopathic hypercalciuria.

Search methods

We searched MEDLINE, EMBASE, the Cochrane Renal Group's specialised register, the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*), handsearched relevant conference proceedings and reference lists of articles.

Selection criteria

All randomised controlled trials (RCTs) and quasi-RCTs that compared any pharmacological intervention for preventing complications in idiopathic hypercalciuria, with placebo, other pharmacological intervention or a different administration mode or dose of the same treatment given for a minimum duration of four months and had a follow-up period of at least six months.

Data collection and analysis

Four authors assessed the studies for inclusion and extracted the data. Disagreements were resolved through discussion. Results were expressed as risk ratios (RR) with 95% confidence intervals (CI) or mean difference (MD).

Main results

Five studies (316 adult patients) were included. Four compared thiazides with standard treatment (periodic clinical follow-up and increased water intake) or specific dietary recommendations and one analysed the effect of thiazide plus a neutral potassium salt. There was a significant decrease in the number of new stone recurrences in those treated with thiazides (RR 1.61, 95% CI 1.33 to 1.96), although the

follow-up periods varied. The stone formation rate also showed a statistically significant decrease in the patients treated with diuretics (MD -0.18, 95% CI -0.30 to -0.06). Thiazides plus potassium salts significantly decreased calciuria and vitamin D levels.

Authors' conclusions

There is some evidence that in patients with idiopathic hypercalciuria and recurrent stones, the addition of thiazides to a normal or modified diet for short to long periods (five months to three years) reduced the number of stone recurrences and decreased the stone formation rate. Thiazides and neutral potassium phosphate decreased calciuria in symptomatic patients with idiopathic hypercalciuria. There were no studies investigating the effect of pharmacological treatment on other clinical complications or asymptomatic idiopathic hypercalciuria.

PLAIN LANGUAGE SUMMARY

Pharmacological interventions for preventing complications in idiopathic hypercalciuria

Idiopathic hypercalciuria is an inherited metabolic abnormality characterised by excessive amounts of calcium excreted into the urine in patients with normal serum levels of calcium. The main complications of this disease in adults are the formation of kidney stones and bone loss. In children, hypercalciuria can cause recurrent haematuria (blood in the urine), frequency-dysuria syndrome (frequent painful or difficult urination), urinary tract infection and abdominal and back pain. The aim of this review was to evaluate the benefits and harms of drug treatments for preventing the complications of idiopathic hypercalciuria. We identified four studies comparing thiazides (diuretics) with either standard treatment of clinical follow-up and increased water intake or specific dietary recommendations and one study comparing thiazides plus a potassium salt. There was a decrease in the number of new stones in the group receiving thiazides as well as an increase in the time taken for new stone formation. The addition of potassium salts to thiazide treatment significantly reduced the amount of calcium excreted in the urine. No studies in children were identified and there were no studies investigating the use of drug treatment for those with hypercalciuria but were symptom free.

BACKGROUND

Idiopathic hypercalciuria is defined as calcium excretion greater than 0.1 mmol/kg/24 h in patients with an unrestricted calcium diet and with no evidence of secondary causes, such as primary hyperparathyroidism, renal tubular acidosis, malignancy, vitamin D intoxication, immobilization, hyperthyroidism or Bartter's syndrome (Langman 1984). Idiopathic hypercalciuria is one of the most common hereditary metabolic anomalies, to such an extent that prevalence rates in the healthy population have been reported to be between 2.9% and 6.5% (García-Nieto 2000).

The physiopathology of idiopathic hypercalciuria is highly complex. Hypercalciuria has been attributed to numerous factors that affect the calcium-phosphorus metabolism. There are three main physiopathological mechanisms:

1. reduction in the tubular reabsorption of calcium, with the emergence of compensatory hyperparathyroidism (Coe 1988);
2. an increase in, or hypersensitivity to, the intestinal reabsorption of calcium secondary to high levels of calcitriol (Pak 1979); and
3. renal loss of phosphates with secondary increased synthesis of calcitriol and intestinal hyperabsorption (Navarro 1994).

When concentrations of calcium and oxalate reach saturation, stones begin to form with the association of small amounts of crystalloid that form nuclei. These nuclei normally grow and aggregate on surfaces such as collecting ducts and renal papillary epithelium. Fortunately, stone formation is inhibited in urine by substances that prevent crystallisation (magnesium, citrate, pyrophosphate). Therefore, crystallisation in undiluted human urine will begin only in a supersaturated solution of calcium and oxalate. About 80% of all kidney stones contain calcium, and at least 40% to 60% of all calcium stone formers are found to have hypercalciuria when tested (Lerolle 2002). Hypercalciuria contributes to kidney stone disease in adults and children (Stapleton 1987). In industrialised nations, renal stones occur in 15% of men and 6% of women and recur in approximately half (Bihl 2001).

The morbidity of urinary tract calculi is primarily due to obstruction with associated pain, although it is well recognized that non-obstructing calculi can still produce considerable discomfort. On the other hand, obstructing calculi can be asymptomatic, which is the typical scenario in the unusual patient who suffers renal loss from chronic, untreated obstruction. Haematuria caused by stones, while frightening to the patient, is rarely dangerous in itself. In children, hypercalciuria can cause a wide variety of symptoms, the most common of which is recurrent haematuria (macroscopic or microscopic). Haematuria is thought to be caused when calcium oxalate injures the uro-endothelium: it is self-limited and it is not accompanied by proteinuria (Garcia 1991). Other common clinical manifestations are frequency-dysuria syndrome and abdominal and lumbar pain. Its association with recurrent urinary infections has also been described (Vachvanichsanong 2001). The most morbid and potentially dangerous aspect of stone disease is the combination of obstruction and infection of the upper urinary tract. Pyelonephritis, pyonephrosis (gross pus in the renal collecting system) and urosepsis can ensue (Leslie 2000).

Another problem with hypercalciuria is its possible relationship with osteopenia and osteoporosis, especially when due to

renal-leak hypercalciuria. The extra calcium required for renal excretion is drawn from the bones and eventually reduces bone density (Asplin 2003; Freundlich 2002). Up to 30% of children with idiopathic hypercalciuria have osteopenia, the long-term seriousness of which has yet to be determined (García-Nieto 1997). Numerous pharmacological treatments have been described that can decrease levels of calciuria or its index of urinary crystallization, although its real role in controlling the illness and preventing its clinical manifestations is controversial. Thiazide has been shown to correct the renal-leak of calcium by increasing calcium reabsorption in the distal tubule, depleting extracellular volume and stimulating calcium reabsorption in the proximal tubule.

Many studies have analysed how efficient diuretics are at preventing the recurrence of idiopathic calcium stones, although very few have focused on patients with proven hypercalciuria (Pearle 1999). As the underlying cause of most calcium stones is hypercalciuria, it may be possible to extrapolate some of the results, although further in-depth studies are required. Thiazides can cause hypokalaemia, which in turn leads to the appearance of intracellular metabolic acidosis and hypocitraturia. Indapamide, a non-thiazide diuretic, seems to have similar effects, although with fewer side effects (Borghi 1993). Thiazides have been shown to be useful for recovering bone mass in patients with recurrent stones and hypercalciuria, although the long-term effect of this pharmacological measure is still not very clear.

Potassium citrate has an inhibitory activity on calcium oxalate, crystallization, aggregation and agglomeration and it has given good results in patients with hypocitraturia (Barcelo 1993). A new salt, potassium-magnesium citrate, seems to be effective at decreasing the recurrence of calcium stones in patients with no specific metabolic disorder (Ettinger 1997). Its possible beneficial effect on recovering bone mass is not clear. Allopurinol, a xanthine oxidase inhibitor, reduces uric acid synthesis and lowers urinary uric acid. It has proven to be effective at reducing the recurrence of calcium stones only in those patients with marked hyperuricosuria and normocalciuria, but not in those with non-specific calcium stones or with hypercalciuria (Ettinger 1976; Wilson 1984).

Orthophosphates reduce vitamin D levels, which leads to a subsequent reduction in urinary calcium excretion. They also increase urinary levels of pyrophosphate and citrate, which increases the inhibitory capacity. Despite these properties, the studies have not been able to show conclusively any beneficial effect on the recurrence of stones. Their theoretical benefit on the recovery of bone mass is not conclusive either (Breslau 1995; Ettinger 1976; Ullmann 1984). Such other drugs as bisphosphonates (Bushinsky 1999; Ruml 1995), sodium cellulose phosphate (Hayashi 1975), and dipyridamole (Michaut 1994) have either not been shown to be effective at preventing stones or have considerable adverse effects.

One problem that most studies that analyse the effectiveness of drug treatments on renal stones must deal with is that the course of the disease is slow and variable. The average rate of stone formation in recurrent stone formers is approximately 0.15 to 0.20 stones/year (Tiselius 2000). This means that a study that attempts to demonstrate the efficacy of specific treatment programmes must last for some years.

OBJECTIVES

- To assess the efficacy, effectiveness and safety of pharmacological interventions for preventing complications in idiopathic hypercalciuria (urinary stones and osteopenia) in adults and children.
- To assess the benefits of pharmacological interventions in decreasing urological symptoms in adults and children with idiopathic hypercalciuria.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (e.g. allocation using alternation, case record numbers, date of birth or day of the week) that compare the efficacy of pharmacological interventions at preventing complications in idiopathic hypercalciuria.

Types of participants

Inclusion criteria

Studies performed on adults and children with idiopathic hypercalciuria undergoing pharmacological treatment to control the illness and its complications.

Exclusion criteria

Patients with secondary hypercalciuria or suffering other illnesses that could cause osteopenia or urinary stones were excluded.

Types of interventions

- Studies testing any pharmacological intervention for preventing complications in idiopathic hypercalciuria, comparing it to placebo, other pharmacological intervention or a different administration mode or dose of the same treatment.
- We assessed only those interventions that had a minimum duration of four months and a follow-up period of at least six months.

Types of outcome measures

Primary outcomes

- Reduction in stone formation (stone rate or calcium stone recurrences or increase in stone-free patients). Stone rate is defined as the number of stones/patient/year. A new stone was defined by radiography, ultrasonography or pyelography as all patients were stone-free before therapy.
- Increase or no reduction in bone mass: Dual-energy X-ray, absorptiometry over a minimum of six months.
- Reduction in urinary symptoms (incidence of urinary tract infection (UTI), haematuria, dysuria, enuresis) over a minimum of six months.
- Improvement in quality of life in terms of days in hospital, days off work or days off school.

Secondary outcomes

- Reduction in calciuria (decrease in 24 hour calciuria or urinary calcium/creatinine ratio).

- Reduction in creatinine clearance.

Adverse clinical reactions

- Gastrointestinal side effects.
- Increased levels of cholesterol and triglycerides.
- Changes in blood pressure.
- Reduction in serum 1,25 dihydroxyvitamin D.
- Fluid/electrolyte imbalance (hyponatraemia, hypercalcaemia, hyperuricaemia, hypokalaemia, hypermagnesaemia, hyperchloraemia, acidosis, hyperglycaemia, hypocitraturia).

Search methods for identification of studies

Relevant studies were obtained from the following sources (see [Appendix 1](#) for electronic search terms).

Electronic searches

1. Cochrane Renal Group's specialised register (May 2008)
2. Cochrane Central Register of Controlled Trials (CENTRAL, in *The Cochrane Library*, Issue 2, 2008).
3. MEDLINE (1966 to May 2008) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs ([Dickersin 1994](#)) with a specific search strategy for developed with input from the Cochrane Renal Group Trial Search Coordinators.
4. EMBASE (1980 to May 2008) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of RCTs ([Lefebvre 1996](#)) together with a specific search strategy developed with input from the Cochrane Renal Group Trial Search Coordinators.

Searching other resources

1. Reference lists of nephrology textbooks, review articles and relevant studies.
2. Reference lists of abstracts from nephrology scientific meetings.
3. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Screening for eligibility

The study was undertaken by five authors (JE, AB, FP, AF, MR). The search strategy described was used to obtain titles and abstracts of studies that could be relevant to the review. The titles and abstracts were screened independently by the authors, who discarded studies that were not applicable, however studies and reviews that might include relevant data or information were retained initially. Authors independently assessed retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria. Data extraction was carried out by the same authors independently using standard data extraction forms. Studies not reported in English or Spanish were translated before assessment. Where more than one publication of one study existed, only the publication with the most complete data was included. Any further information required from the original author was requested by written correspondence and any relevant information obtained in this manner was included in the review. Disagreements were resolved in consultation with MR.

Assessment of methodological quality

The quality of studies included was assessed independently by JE, AB, FP and AF without blinding to authorship or journal using the checklist developed for the Cochrane Renal Group. Discrepancies were resolved by discussion with MR. The quality items assessed were allocation concealment, intention-to-treat analysis, blinding of investigators, participants, outcome assessors and data analysis and completeness to follow-up.

Quality checklist

Allocation concealment

- Adequate (A): Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study
- Unclear (B): Randomisation stated but no information on method used is available
- Inadequate (C): Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group

Blinding

- Blinding of investigators: Yes/no/not stated
- Blinding of participants: Yes/no/not stated
- Blinding of outcome assessor: Yes/no/not stated
- Blinding of data analysis: Yes/no/not stated

The above are considered not blinded if the treatment group can be identified in > 20% of participants because of the side effects of treatment.

Intention-to-treat analysis

- Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
- Yes: not specifically reported but confirmed upon study assessment.
- No: Not reported and lack of intention-to-treat analysis confirmed on study assessment. (Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation).
- No: Stated but not confirmed upon study assessment.
- Not stated.

Completeness to follow-up

Per cent of participants excluded or lost to follow-up.

Data analysis

For dichotomous outcomes (new stones, osteopenia, haematuria, frequency-dysuria syndrome, UTI, gastrointestinal side effects) results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Data were pooled using the random effects model but the fixed effects model was also analysed to ensure robustness of the model chosen and susceptibility to outliers. Where continuous scales of measurement were used to assess the effects of treatment (decrease in 24 hour calciuria or urinary calcium/creatinine ratio, blood pressure, serum creatinine,

serum cholesterol and triglycerides, serum 1,25-dihydroxyvitamin D, natraemia, calcaemia, uricaemia, magnesemia, chloraemia, acidosis, glycaemia, oxaluria and citraturia), the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales were been used. Heterogeneity was assessed with the I^2 test (Higgins 2003) and with a Chi squared test with a P value < 0.10 indicating statistical significance. I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

RESULTS

Description of studies

We identified 24 studies that compared pharmacological interventions for preventing complications in idiopathic hypercalciuria. Nineteen did not meet the inclusion criteria (Brocks 1981; Cicerello 1994; Coe 1988; Ettinger 1988; Ettinger 1997; Heller 1998; Herrmann 1999; Jaeger 1986; Jaipakdee 2004; Jiménez Verdejo 2001; Kato 2004; Laerum 1984; Legroux-Gerot 2004; Martins 1996; Mortensen 1986; Parks 2003; Reusz 1998; Smith 1983; Soygür 2002). The reasons for these exclusions are listed in the table *Characteristics of excluded studies*. Four studies that included hypercalciuric patients had to be excluded because we could not obtain data on this subgroup after contact with the authors (Ettinger 1988; Ettinger 1997; Jaipakdee 2004; Soygür 2002).

Five studies were included (Ala-Opas 1987; Borghi 1993; Breslau 1995; Fernández-Rodríguez 2006; Ohkawa 1992). All were parallel RCTs. The outcomes were assessed at the end of the intervention in three studies (Borghi 1993; Breslau 1995; Fernández-Rodríguez 2006), while in Ala-Opas 1987 and Ohkawa 1992 a longer period of follow-up was established. A total of 529 patients were recruited (adults only, no children) of whom 316 had idiopathic hypercalciuria and were analysed in this review. The studies were classified into two comparisons depending on the pharmacological agents studied. Four studies compared an agent of the thiazide family with a control intervention (Ala-Opas 1987; Borghi 1993; Ohkawa 1992; Fernández-Rodríguez 2006), and one study compared potassium phosphate with placebo (Breslau 1995). Borghi 1993 examined the effect of indipamide and has been included with the thiazides comparison because this agent, despite having its own characteristics, can be assimilated into the thiazide family.

- Fernández-Rodríguez 2006 compared three groups of 50 patients suffering from recurring stones who were followed up closely, treated with 50 mg/d of hydrochlorothiazide (group 1) and 50 mg/d of hydrochlorothiazide plus 20 mEq/d of potassium citrate (group 2). We have analysed the subgroup of patients with idiopathic hypercalciuria from the two pharmacologically treated groups (17 and 21 patients, respectively).
- Ala-Opas 1987 compared the effect of a daily intake of 40 g of bran and a similar intermittent intake of bran plus hydrochlorothiazide (from May to September) in a subgroup of 32 patients with absorptive hypercalciuria.
- Borghi 1993 compared the diuretic drug indapamide in conjunction with a specific diet and the effect of diet only. The diet was the same for all the participants in the study and consisted of avoiding a high intake of salt (120 to 140 mEq/d) and reducing the intake of calcium (400 to 600 mg/d), oxalate (40 to 60 mg/d) and purines (200 to 400 mg/d). A high fluid intake was also recommended of non-mineral waters. The patients with

idiopathic hypercalciuria and recurrent stones were randomised into three groups of 25. The first group was put on the diet alone, the second group was put on the diet and also treated with indapamide for three years. The third group was put on the diet and also treated with indapamide and allopurinol. We compared only the first two groups to assess the effect of the diuretic drug on the appearance of stones or the metabolic effect.

- [Ohkawa 1992](#) was carried out in an extensive series of 210 patients with idiopathic hypercalciuria and stones. The effect of treatment with trichlormethiazide was compared with follow-up, without placebo. The follow-up time varied between 6 months and 5.7 years.
- [Breslau 1995](#) analysed the hypocalciuric effect of a slow-release neutral potassium phosphate salt in comparison to a placebo for a period of three months, in a group of 31 patients with idiopathic hypercalciuria.

Risk of bias in included studies

Potential for selection bias at study entry (randomisation and allocation concealment)

All five studies stated that participants had been randomised. However, none described an adequate method of allocation concealment.

Potential for bias at time of treatment or outcome assessment (blinding of participants, care givers, outcome assessors)

[Breslau 1995](#) reported that the participants and researchers had been blinded. None of the studies reported blinding of the outcome assessors.

Potential for bias in trial analysis (withdrawals and intention-to-treat analysis)

In two studies the length of intervention and follow-up were the same (three years).

- [Fernández-Rodríguez 2006](#) reported no withdrawals or dropouts
- [Borghi 1993](#) reported 11/75 patients were lost to follow-up and an intention-to-treat analysis was not performed.

In the other three studies the length of intervention and follow-up varied.

- In [Ala-Opas 1987](#), the intervention lasted five months and follow-up lasted two years and no withdrawals or dropouts were reported.
- [Ohkawa 1992](#) recruited 210 patients. The mean length of intervention and follow-up ranged between 6 months and 5.7 years. A total of 35 participants dropped out and the reasons were described. However, the lost patients were not included in the final analysis, so they did not perform an intention-to-treat analysis.
- [Breslau 1995](#) included 31 participants, only lasted three months, and there were no withdrawals or dropouts. This study was finally included in the review, despite its short follow-up, because of its quality and the fact that it introduced an original treatment, exclusively to assess the secondary outcomes for our review.

Effects of interventions

Thiazide versus other interventions

We analysed the four studies that compared the effect of thiazides (including [Borghi 1993](#) who used indapamide) with the standard control of the disease (periodic clinical follow-up and general recommendation for increasing water intake) or specific dietary recommendations ([Ala-Opas 1987](#); [Borghi 1993](#); [Fernández-Rodríguez 2006](#); [Ohkawa 1992](#)).

Kidney stones

The recurrence of kidney stones was assessed in four studies ([Ala-Opas 1987](#); [Borghi 1993](#); [Fernández-Rodríguez 2006](#); [Ohkawa 1992](#)), with a total of 285 patients. In all studies, the association of thiazide diuretics with strategies for the dietary control of the recurrence of stones improved results. We assessed the total number of patients who had no new recurrences during the follow-up period and found that there was a significant decrease in those who had been treated with thiazides ([Analysis 1.1](#): RR 1.61, 95% CI 1.33 to 1.96). Although the follow-up periods were not homogeneous, particularly in [Ohkawa 1992](#), there was no significant heterogeneity ($I^2 = 0\%$). This protector effect was present when combining the results of the three studies using classic thiazides ([Analysis 1.1 .1](#): RR 1.64, 95% CI 1.27 to 2.13), while the study using indapamide did not reach statistical significance ([Analysis 1.1 .2](#): RR 1.47, 95% CI 0.97 to 2.24).

To assess the number of recurrences of kidney stones, noting that some patients had multiple recurrences, we also looked at the stone formation rate. In the three combined studies ([Ala-Opas 1987](#); [Borghi 1993](#); [Ohkawa 1992](#)) there was a statistically significant decrease in the number of stones/patient/year in those treated with diuretics ([Analysis 1.2](#): MD -0.18, 95% CI -0.30 to -0.06; $I^2 = 0\%$). When analysed separately this effect can be seen in the combination of classic thiazides studies ([Analysis 1.2 .1](#): MD -0.16, 95% CI -0.30 to -0.03), but again it was not statistically significant in the study using indapamide ([Analysis 1.2 .2](#): MD -0.22, 95% CI, -0.46 to 0.02).

[Ala-Opas 1987](#) provided data that examined the protective effect of thiazides on stone relapse ([Analysis 1.3](#): MD 0.23, 95% CI -0.41 to 0.87).

Urinary calcium levels

We have not analysed the combined results of the four studies because the effect was not measured with comparable parameters. [Fernández-Rodríguez 2006](#) gave no detailed data about the quantification of the calciuria, but a dichotomised study was carried out on the number of patients that have high levels of calcium secretion throughout their treatment with diuretics. They reported the treatment with thiazides decreased the number of patients with high levels of urinary calcium excretion by 57% (95% CI 24% to 76%), an effect that was maintained for three years.

[Ohkawa 1992](#), carried out in an extensive series of patients with idiopathic hypercalciuria and stones, compared the effect of trichlormethiazide treatment with follow-up alone. The follow-up time varied between six months and four years, and the data analysed showed a decrease in calciuria measured by the calcium/creatinine excretion ratio (mol/mol) at one month and one, three and four years. There was no significant decrease at two years. In the control group, although the excretion figures fluctuate, no significant differences were found with the initial baseline figures.

[Borghi 1993](#) quantified a significant decrease in 24 hour calciuria in the group treated with indapamide throughout the follow-up period. The effect lasted up to 36 months and the mean decrease was 48% ([Analysis 1.4](#): MD -129 mg/24 h, 95% CI -184.21 to -73.79). Oxaluria decreased significantly in comparison to its baseline values in the patients treated with indapamide, however there was no significant difference between the indapamide/diet group and diet group alone at the end of the follow-up period ([Analysis 1.5](#): MD -3.0 mg/24 h, 95% CI -7.06 to 1.06). The calcium oxalate relative supersaturation index and the calcium phosphate relative supersaturation index decreased significantly throughout the study, which reflects a decrease in the risk of urinary crystallization and indirectly may decrease the risk of urinary stones.

In [Ala-Opas 1987](#), the addition of thiazides did not significantly decrease calciuria when compared to bran alone ([Analysis 1.6](#): MD -0.04 mol/mol calcium/creatinine, 95% CI -0.11 to 0.03).

Other results

We have not analysed the combined results of the four studies because the effect was not measured with comparable parameters. For adverse effects, patients treated with indapamide ([Borghi 1993](#)) had lower plasma potassium levels ([Analysis 1.7](#): MD -0.50 mol/L, 95% CI -0.72 to -0.28) and higher uric acid levels than the baseline values but not between groups ([Analysis 1.8](#): MD 0.50 mg/dL, 95% CI -0.15 to 1.15). No alterations were found compared to baseline lipid levels, although the group treated exclusively with the diet had higher triglycerides levels ([Analysis 1.10](#): MD -42.00 mg/dL, 95% CI -73.73 to 10.27). There was no significant difference in serum cholesterol levels ([Analysis 1.9](#): MD -21.00 mg/dL, 95% CI -56.35 to 14.35).

[Ohkawa 1992](#) showed that during the follow-up period, the urinary levels of magnesium and phosphorus were similar in both groups. Only one patient in the thiazide group presented with temporary hypokalaemia and three others presented with hyperuricaemia in an isolated check-up (versus no patient in the control group). [Fernández-Rodríguez 2006](#) provides no data on adverse effects but stated that there was less need for extracorporeal lithotripsy to remove the stones in the thiazide group. The difference between the two groups was statistically significant (6/17 in the control group and 4/21 in the thiazide group).

Potassium phosphate versus placebo

In a group of 31 patients with idiopathic hypercalciuria, [Breslau 1995](#) analysed the hypocalciuric effect of a slow-release neutral potassium phosphate salt in comparison to placebo for a period of three months. Potassium phosphate decreased the excretion of urinary calcium ([Analysis 2.1](#): MD -86.00 mg/24 h, 95% CI -118.36 to -53.64); fasting calcium/mg/dL glomerular filtrate ([Analysis 2.4](#): MD -0.03, 95% CI -0.05 to -0.01) as well as the intestinal calcium absorption rate ([Analysis 2.5](#): MD -7%, 95% CI -12.99 to -1.01). However the levels of urinary citrate do not change ([Analysis 2.2](#): MD 102.00 mg/24 h, 95% CI -45.56 to 249.56), and neither did those of oxalate or uric acid. No differences were found between the hormones that regulate calcium absorption and the parathyroid hormone. The plasma levels of 1,25 dihydroxyvitamin D decreased significantly with respect to the baseline levels in the patients treated with potassium phosphate (50 ± 11 versus 42 ± 9), although these differences were not seen between groups ([Analysis 2.3](#): MD -5.00 pg/mL, 95% CI -12.28 to 2.28). The markers of bone

reabsorption change slightly from their baseline values: alkaline phosphatase and serum procollagen decreased in the patients treated with phosphate, and increased in the controls.

Sensitivity analyses

The outcomes that were meta-analysed showed no numerical heterogeneity: $I^2 = 22\%$ in stone-free patients for studies using classic thiazides ([Analysis 1.1](#)) and $I^2 = 0\%$ in stone formation rate ([Analysis 1.2](#)) in studies using thiazides, and thus the sensitivity analysis applying the fixed effects model reached the same results than the more conservative random effects model. There were insufficient data to perform sensitivity analyses on the other outcomes.

DISCUSSION

Idiopathic hypercalciuria is a common inherited metabolic abnormality characterised by excessive amounts of calcium excreted in the urine in patients with normal serum calcium levels. The morbidity of hypercalciuria is related to two main separate factors: kidney stone disease and bone demineralization leading to osteopenia and osteoporosis. Hypercalciuria contributes to kidney stone disease in adults and children. Patients with hypercalciuria form kidney stones of oxalate and calcium phosphate. In some cases crystallized calcium can be deposited in the renal interstice causing calcification of the kidney. In children, hypercalciuria can cause a wide variety of symptoms, the most common of which is recurrent haematuria (macroscopic or microscopic), but can also produce frequency-dysuria syndrome, urinary tract infection and abdominal and lumbar pain.

Metabolic control

We analysed the various pharmacological strategies for clinically controlling the disease to see if it is possible to metabolically control the disease and decrease the levels of excretion of urinary calcium.

The drugs most commonly used for the pharmacological control of idiopathic hypercalciuria were thiazide diuretics because of their well-known effect on decreasing calciuria. We were not able to analyse the data from some studies because of the heterogeneous presentation of the results, but in all of them the favourable result was statistically significant.

We questioned whether this effect would last or whether its effectiveness would decrease over time. In two studies ([Borghi 1993](#), [Fernández-Rodríguez 2006](#)), we saw that the hypocalciuric effect of the thiazides is considerable (mean decrease of almost 48%) and this was maintained for at least three years. Indapamide also decreased the levels of oxaluria after prolonged periods of treatment, reducing the calcium oxalate relative supersaturation index and the calcium phosphate relative supersaturation index, and therefore also the risk of the calcium crystallizing in the urine ([Borghi 1993](#)). In a small group of patients monitored for four years, [Ohkawa 1992](#) reported a similar finding. [Fernández-Rodríguez 2006](#) also analysed how many patients become normocalciuric with thiazide treatment (60% of the patients studied). [Ala-Opas 1987](#), who administered thiazides intermittently with bran, also obtained considerable reductions with respect to baseline figures but they were not greater than the reductions with bran by itself, which has the well-known effect of interfering with the intestinal absorption of both lipids and calcium. In these studies, we can conclude that the

hypocalciuric effect of thiazide diuretics has been well established in patients with idiopathic hypercalciuria and that, although the size of the effect is variable, it can be maintained for at least three years.

[Breslau 1995](#) analysed the hypocalciuric effect of a slow release, neutral potassium phosphate salt in patients with idiopathic hypercalciuria. The drug significantly decreases calciuria and vitamin D levels. It also had a modest effect on improving the markers of bone turnover and on the index of intestinal absorption of calcium. This drug seems to have a beneficial effect on the metabolic control of idiopathic hypercalciuria (although the results were observed in a short follow-up of three months). This RCT was included in the review in order to assess the effect of the only drug we found other than thiazides, although it did not fulfil the requirements of carrying out a long-term follow-up and analysing the effect on clinical complications.

Clinical efficacy

Kidney stones

Kidney stones are the main clinical manifestation of idiopathic hypercalciuria and have the greatest associated morbidity. Most of the clinical studies carried out have focused on this aspect and they all have used different combinations of thiazide diuretic drugs, during variable periods of time, to evaluate the extent of their protective effect against stones. This seems logical, given their good metabolic control of hypercalciuria. We included only those RCTs that had a follow-up longer than six months and which distinguished those patients with idiopathic hypercalciuria among all the patients with calcium stones. This selection enabled us to work with a total of four RCTs and a total of 285 patients.

We analysed RCTs that compared the effect of thiazides with the standard means for controlling the disease or with specific associated dietetic recommendations. The results of this meta-analysis showed that the use of diuretics could reduce the rate of recurrence of stones. The index of stone-free patients had a RR of 1.61 (95% CI 1.33 to 1.96), indicating that the use of thiazides can keep more patients from suffering further episodes of stones for up to three years. We also analysed the stone formation rate because it gave us an idea of the number of stones that appear in the series/patient and year, and gave us more information about how a treatment reduces the total number of stones, including those patients with multiple recurrences. The combined value of this index from three studies also showed that the associated use of diuretics gives favourable results, with a MD of -0.18 stones/patient/year (95% CI -0.30 to -0.06).

We tried to weight the effect of the classical thiazides used alone or in combination with specific dietetic measures. To do so, we selected those patients with idiopathic hypercalciuria who compared the use of classical thiazides with general follow-up measures with or without specific diet. The results of the meta-analysis show that the prolonged use of this type of thiazide had a favourable effect. The rate of recurrence of stones could be reduced significantly. Patients treated with thiazides remained free of new stones (stone-free patients) with an RR of 1.64 (95% CI 1.27 to 2.13) which meant that thiazides had a protective effect with an NNT of 3 (2 to 5). Nevertheless, this apparently important protective effect should be carefully considered given the quality of the original studies that did not use placebo in their

comparisons and the precaution that must be exercised with NNTs obtained from a combination of studies. [Fernández-Rodríguez 2006](#) describes no losses and the follow-up period is homogeneous (36 months) for all the participants, even though the cases come from a subgroup analysis (patients with recurrent calcium stones and hypercalciuria). On the other hand, in [Ohkawa 1992](#) the mean follow-up period was 2.21 years (SD 1.37) in the thiazide group and 2.14 (SD 1.33) in the control group. Therefore, if the individual follow-up period for each patient is not taken into account, the effect of the treatment may be exaggerated if a particular patient has short follow-up periods. The results provided by [Ohkawa 1992](#) may be of extra value because they evaluated the protective effect of thiazides on the basis of stone formation rate (number of stones/patient/year), which was lower in the group receiving thiazides (0.13 versus 0.31) with statistically significant differences.

Another important clinical consideration is that the group treated with diuretics had less need of extracorporeal shock wave lithotripsy to eliminate the stones ([Fernández-Rodríguez 2006](#)). This may indicate that the new stones formed in the treatment group were smaller in size and clinically easier to handle. If proven, then the use of thiazides for a prolonged period of time may reduce the rate of recurrence and, therefore, have a beneficial effect on the control of the disease.

[Ala-Opas 1987](#) compared the intermittent administration of hydrochlorothiazide (taken for 5/24 months) and bran with the administration of bran alone. Both strategies reduced calciuria and the recurrence of stones, although statistical significance was not reached.

Indapamide is the first of a new class of oral antihypertensive/diuretics, the indolines. We included it in the group of thiazide diuretics because, although chemically different, it shares most of its mechanisms of action. We have separately analysed the effect of indapamide on the metabolic control of idiopathic hypercalciuria ([Borghi 1993](#)). In addition, [Borghi 1993](#) made some general dietary recommendations for all the participants: avoid a high intake of salt; reduce the intake of calcium, oxalate and purines; and consume only small quantities of unmineralised water. Two of the groups were treated with indapamide or indapamide and allopurinol, while a third group were treated by diet alone. There was a significant decrease in the stone formation rate from the baseline value of 1.41 to 0.06 after treatment in the group treated with indapamide. This decrease is much greater than any decrease obtained with dietary measures alone (0.28). For the index of stone-free patients, the group treated with indapamide obtained significantly better results than the group treated by diet alone. A total of 84.2% of the patients in the indapamide group had no recurrences compared to 57.2% of patients in the diet group. Indapamide seems to increase the effect of diet on the reduction in stone recurrence.

The use of thiazide diuretics to control the recurrence of urinary stones in patients with idiopathic hypercalciuria, with or without specific dietary measures seems to be beneficial and considerably reduces the number of episodes of stones. These results should be considered with some caution. Apart from the possibility of publication bias, the studies are small with certain methodological shortcomings and used different thiazide drugs for different periods of time.

The adverse effects caused by the prolonged use of thiazide diuretics seem to be minor in the studies analysed. [Borghi 1993](#) described a slight decrease in the plasma levels of potassium and an increase in uric acid with respect to baseline values. These changes do not reach clinical significance. There was no difference in the plasma levels of cholesterol, glucose and triglycerides between patients treated with thiazides and patients on the specific diet. Most studies do not describe any outstanding adverse effects, which may be due to the lack of information or because they are only of minor clinical relevance.

We also analysed the use of other drugs in association with thiazides to boost their effect. [Borghi 1993](#) combined allopurinol with indapamide with the aim to decrease urinary uric acid in patients with idiopathic hypercalciuria and normal urinary uric acid levels. This combination decreased the plasma and urinary levels of uric acid but did not improve the rate of recurrence of stones in patients treated intermittently with indapamide. [Fernández-Rodríguez 2006](#) combined potassium citrate with hydrochlorothiazide in a subgroup of patients. This combination reduced both the rate of recurrence and the number of patients who require lithotripsy to eliminate stones, although none of these results reach statistical significance because of the small size of the sample. It seems plausible that the addition of potassium citrate, which can alkalinise the urine and decrease the capacity of calcium to crystallize, would be beneficial, but more extensive studies are required if this effect is to be demonstrated.

Other clinical manifestations

For the control of osteoporosis and osteopenia associated with idiopathic hypercalciuria a few reports on a small series patients highlighted a possible beneficial effect of treatment with etidronate and calcium supplementation ([Heilberg 1998](#)) or with thiazides ([Adams 1999](#); [Reusz 1998](#); [Van Faassen 1998](#)), which led to an increase in bone mass. Nevertheless, to date, no RCTs have been carried out to confirm these preliminary findings. Some studies suggest that potassium citrate or thiazides are effective at decreasing the symptoms associated to crystalluria in children ([Alon 1990](#); [Lopez 1999](#)), again there have been no RCTs undertaken to confirm these findings.

Patients with asymptomatic idiopathic hypercalciuria

It would be of interest to determine whether patients affected by idiopathic hypercalciuria, most of whom are asymptomatic, would benefit from preventive treatment to avoid the onset of stones or osteopenia. We have not found any RCT or cohort study that deals with this issue. We believe this important and that it would be logical to begin studies to investigate the possible beneficial effects of metabolic control in asymptomatic idiopathic hypercalciuria for preventing possible complications.

AUTHORS' CONCLUSIONS

Implications for practice

- There is some evidence of moderate quality that, in patients with idiopathic hypercalciuria and recurrent stones, the addition of thiazide diuretics to a usual or modified diet for short to long periods (five months to three years) reduces the number of recurrences of stones and decreases the stone formation rate in comparison to other treatment strategies.
- There is some evidence of moderate quality that both thiazide diuretics and neutral potassium phosphate can decrease calciuria in symptomatic patients with idiopathic hypercalciuria, without presenting any outstanding adverse effects.
- There is no evidence of the effect of pharmacological treatment for preventing the formation stones or asymptomatic idiopathic hypercalciuria patients.

Implications for research

More well designed, adequately powered RCTs are required in patients with idiopathic hypercalciuria to determine whether there are other effective treatments for controlling or preventing kidney stones and other clinical manifestations, particularly osteopenia. The issue of asymptomatic idiopathic hypercalciuria patients needs to be addressed so that the possibility of long-term metabolic control for preventing the appearance of clinical manifestations can be assessed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ala-Opas 1987

Methods	Controlled, parallel RCT Not blinded
Participants	Subgroup of 32 patients with hypercalciuria out of 73 recurrent stone formers. Sex: 60 men, 13 women Mean age: 48 years
Interventions	Group A Number: 18 Treatment: Bran (40 g/d) Group B Number: 14 Treatment: Bran (40 g/d) + thiazide (50 mg twice a day)
Outcomes	<ul style="list-style-type: none"> Stone formation rate (stone/year/patient) Stone-free patients (%) Mean urinary excretion of calcium, magnesium, sodium and oxalate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Borghi 1993

Methods	Controlled, parallel RCT Not blinded
Participants	75 patients recurrent stone formers with hypercalciuria Group A Number: 25 Sex: 5 females, 20 males Mean age: 42.8 ($\pm$ 11.3) years Group B Number: 25 Sex: 7 females, 18 males Mean age: 46.5 ($\pm$ 11.4) years Group C Number: 25 Sex: 4 females, 21 males Mean age: 46.2 ($\pm$ 11.6) years
Interventions	Group A

Borghi 1993 (Continued)

Diet and fluid treatment

Group B

Diet and fluid treatment + indapamide (2.5 mg/d)

Group C

Diet and fluid treatment + indapamide (2.5 mg/d) + allopurinol (300 mg/d)

Outcomes	<ul style="list-style-type: none"> Stone formation rate (stones/patient/y) Stone-free patients (%) Reduction in calciuria and oxaluria
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Breslau 1995

Methods	Placebo controlled, parallel, RCT Double blind
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Participants	<p>21 patients recurrent stone formers with hypercalciuria.</p> <p>Group A Number: 9 men Mean age: 46.9 ($\pm$ 12.6) years, range 24 to 62.</p> <p>Group B Number: 12 men Mean age: 48.2 ($\pm$ 13.7) years, range 32 to 73.</p>
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Interventions	<p>Group A Placebo (4 tablets, twice a day)</p> <p>Group B uroPhos-K (4 tablets, twice a day)</p>
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Outcomes	<ul style="list-style-type: none"> Reduction in calciuria Intestinal calcium absorption Fasting calcium/mg/dL glomerular filtrate
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Fernández-Rodríguez 2006

Methods	Controlled, parallel RCT Not blinded
Participants	Subgroup of 52 patients with hypercalciuria out of recurrent stone formers
Interventions	<p>Group A Number: 17 Treatment: No specific therapy</p> <p>Group B Number: 21 Treatment: Hydrochlorothiazide (50 mg/d)</p> <p>Group C Number: 14 Treatment: Hydrochlorothiazide (50 mg/d) + potassium citrate (20 mL Eq/d)</p>
Outcomes	<ul style="list-style-type: none"> Stone-free patients (%)
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

Ohkawa 1992

Methods	Controlled, parallel RCT Not blinded
Participants	175 patients with hypercalciuria. <p>Group A Number: 93 Sex: 52 males, 41 females Mean age: 46.9 (± 13.8) years, range 17 to 75</p> <p>Group B Number: 82 Sex: 45 males, 37 females Mean age: 48.7 (± 12.3) years, range 16 to 77</p>
Interventions	<p>Group A No specific therapy</p> <p>Group B Trichlormethiazide (4 mg/d)</p>
Outcomes	<ul style="list-style-type: none"> Stone formation rate (stones/patient/y) Stone-free patients (%) Reduction in stone formation Remission rate Total number of newly formed stones

Ohkawa 1992 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Brocks 1981	No patients with hypercalciuria.
Cicerello 1994	It has no studied criteria.
Coe 1988	Not a RCT.
Ettinger 1988	Unable to get data on hypercalciuric patients after contacting the authors.
Ettinger 1997	Unable to get data on hypercalciuric patients after contacting the authors.
Heller 1998	It was an open trial.
Herrmann 1999	No patients with hypercalciuria.
Jaeger 1986	Not a RCT.
Jaipakdee 2004	Unable to get data on hypercalciuric patients after contacting the authors.
Jiménez Verdejo 2001	No patients with hypercalciuria
Kato 2004	No patients with hypercalciuria.
Laerum 1984	Hypercalciuric patients were all treated with hydrochlorothiazide (there were no control arm for that patients)
Legroux-Gerot 2004	Compare patients with hypercalciuria and patients with osteoporosis without hypercalciuria
Martins 1996	Treatment only last three months
Mortensen 1986	There were no patients with hypercalciuria
Parks 2003	Not a RCT.
Reusz 1998	There was no control group
Smith 1983	Large number of lost patients
Soygür 2002	Unable to get data on hypercalciuric patients after contacting the authors.

DATA AND ANALYSES

Comparison 1. Thiazides versus others interventions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stone-free patients	4	285	Risk Ratio (M-H, Random, 95% CI)	1.61 [1.33, 1.96]
1.1 Thiazides	3	245	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.27, 2.13]
1.2 Indipamide	1	40	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.97, 2.24]
2 Stone formation rate (stones/patient/year)	3	247	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.30, -0.06]
2.1 Thiazides	2	207	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.30, -0.03]
2.2 Indapamide (Indapamide+diet-and-fluid versus diet-and-fluid)	1	40	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.46, 0.02]
3 Individual mean reduction of stone formation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Urinary calcium levels (mg/24 h)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Urinary oxalate levels (mg/24 h)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Urinary calcium excretion Ca/creatinine (mmol/mmol)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Serum potassium (mmol/L)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 Serum uric acid (mg/dL)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9 Serum cholesterol (mg/dL)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10 Serum triglyceride (mg/dL)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Thiazides versus others interventions, Outcome 1 Stone-free patients.

Analysis 1.2. Comparison 1 Thiazides versus others interventions, Outcome 2 Stone formation rate (stones/patient/year).

Analysis 1.3. Comparison 1 Thiazides versus others interventions, Outcome 3 Individual mean reduction of stone formation.

Study or subgroup	Bran + thiazide		Bran only		Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)		
Ala-Opas 1987	18	0.5 (1.1)	14	0.3 (0.7)		0.23[-0.41,0.87]
					Favours bran only	Favours bran + thiazide

Analysis 1.4. Comparison 1 Thiazides versus others interventions, Outcome 4 Urinary calcium levels (mg/24 h).

Study or subgroup	Diet & fluid + indapamide		Diet & fluid		Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)		
Borghi 1993	19	201 (81)	21	330 (97)		-129[-184.21,73.79]
					Favs diet & fluid + indapamide	Favs diet & fluid only

Analysis 1.5. Comparison 1 Thiazides versus others interventions, Outcome 5 Urinary oxalate levels (mg/24 h).

Study or subgroup	Diet & fluid + indapamide		Diet & fluid		Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)		
Borghi 1993	19	22 (7)	21	25 (6)		-3[-7.06,1.06]
					Favs diet & fluid + indapamide	Favours Diet & fluid only

Analysis 1.6. Comparison 1 Thiazides versus others interventions, Outcome 6 Urinary calcium excretion Ca/creatinine (mmol/mmol).

Study or subgroup	Bran + thiazide		Bran alone		Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)		
Ala-Opas 1987	14	0.3 (0.1)	18	0.3 (0.1)		-0.04[-0.11,0.03]
					Favours bran + thiazide	Favours bran alone

Analysis 1.7. Comparison 1 Thiazides versus others interventions, Outcome 7 Serum potassium (mmol/L).

Study or subgroup	Diet & fluid + indapamide		Diet & fluid		Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)		
Borghi 1993	19	3.9 (0.4)	21	4.4 (0.3)		-0.5[-0.72,-0.28]
					Favours diet & fluid	Favs diet & fluid + indapamide

Analysis 1.8. Comparison 1 Thiazides versus others interventions, Outcome 8 Serum uric acid (mg/dL).

Study or subgroup	Favs diet & fluid + indapamide		Diet & fluid		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Borghi 1993	19	5.9 (1.1)	21	5.4 (1)		0.5[-0.15,1.15]
Favs diet & fluid + indapamide					-2 -1 0 1 2	Favours diet & fluid

Analysis 1.9. Comparison 1 Thiazides versus others interventions, Outcome 9 Serum cholesterol (mg/dL).

Study or subgroup	Diet & fluid + indapamide		Diet & fluid		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Borghi 1993	19	208 (64)	21	229 (48)		-21[-56.35,14.35]
Favs diet & fluid + indapamide					-100 -50 0 50 100	Favours diet & fluid

Analysis 1.10. Comparison 1 Thiazides versus others interventions, Outcome 10 Serum triglyceride (mg/dL).

Study or subgroup	Diet & fluid + indapamide		Diet & fluid		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Borghi 1993	19	112 (44)	21	154 (58)		-42[-73.73,-10.27]
Favs diet & fluid + indapamide					-100 -50 0 50 100	Favours diet & fluid

Comparison 2. Potassium phosphate versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urinary calcium levels (mg/24 h)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Urinary citrate levels (mg/24 h)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Serum 1,25-dihydroxyvitamin D (pg/mL)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Fasting Ca/mg/dL glomerular filtrate	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Intestinal calcium absorption (%)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Potassium phosphate versus placebo, Outcome 1 Urinary calcium levels (mg/24 h).

Study or subgroup	UroPhos-K		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Breslau 1995	18	166 (43)	13	252 (47)		-86[-118.36,-53.64]
					Favours UroPhos-K	Favours placebo

Analysis 2.2. Comparison 2 Potassium phosphate versus placebo, Outcome 2 Urinary citrate levels (mg/24 h).

Study or subgroup	UroPhos-K		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Breslau 1995	18	673 (198)	13	571 (213)		102[-45.56,249.56]
					Favours placebo	Favours UroPhos-K

Analysis 2.3. Comparison 2 Potassium phosphate versus placebo, Outcome 3 Serum 1,25-dihydroxyvitamin D (pg/mL).

Study or subgroup	UroPhos-K		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Breslau 1995	18	42 (9)	13	47 (11)		-5[-12.28,2.28]
					Favours UroPhos-K	Favours placebo

Analysis 2.4. Comparison 2 Potassium phosphate versus placebo, Outcome 4 Fasting Ca/mg/dL glomerular filtrate.

Study or subgroup	UroPhos-K		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Breslau 1995	18	0.1 (0)	13	0.1 (0)		-0.03[-0.05,-0.01]
					Favours UroPhos-K	Favours placebo

Analysis 2.5. Comparison 2 Potassium phosphate versus placebo, Outcome 5 Intestinal calcium absorption (%).

Study or subgroup	UroPhos-K		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Breslau 1995	18	68 (10)	13	75 (7)		-7[-12.99,-1.01]
					Favours UroPhos-K	Favours placebo

APPENDICES

Appendix 1. Electronic search strategies

Database searched	Search terms
MEDLINE	<ol style="list-style-type: none"> 1. RANDOMISED CONTROLLED TRIAL. pt. 2. CONTROLLED CLINICAL TRIAL. pt. 3. RANDOMIZED CONTROLLED TRIALS/ 4. RANDOM ALLOCATION/ 5. DOUBLE BLIND METHOD/ 6. SINGLE BLIND METHOD/ 7. 1 or 2 or 3 or 4 or 5 or 6 8. ANIMAL/ not HUMAN/ 9. 7 not 8 10. CLINICAL TRIAL. pt. 11. exp CLINICAL TRIALS/ 12. (clin\$ adj25 trial\$).tw. 13. CROSS-OVER STUDIES/ 14. (crossover or cross-over or cross over).tw. 15. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).tw. 16. PLACEBOS/ 17. placebo\$.tw. 18. random\$.tw. 19. RESEARCH DESIGN/ 20. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 21. 20 not 8 22. 9 or 21 23. Hypercalciuria.tw. 24. exp Calculi, Urinary/ 25. (Urinary and (Ston\$ or calcul\$)).tw. 26. Urolithiasis.tw. 27. Treatment/ 28. Drug Therapy/ 29. Prevention/ or Prophylaxis 30. (23 or 24 or 25 or 26) and (27 or 28 or 29) 31. 30 and 22
CENTRAL	<ol style="list-style-type: none"> 1. Hypercalciuria 2. Calculi, Urinary. Explode tree Mesh 3. Urinary and (Ston\$ or calcul\$) 4. Urolithiasis 5. Treatment (MeSH) 6. Drug Therapy (MeSH) 7. Prevention or Prophylaxis(MeSH) 8. (#1 or #2 or #3 or #4) and (#5 or #6 or #7)

WHAT'S NEW

Date	Event	Description
23 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Study selection: JE, AB, FP and AF
- Quality assessment: JE, AB, FP, AF and MR
- Data extraction: JE, AB, FP and AF
- Writing of review: JE, AB, FP, AF and MR

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Hospital Universitari Sant Joan de Reus, Spain.
- Universitat Rovira i Virgili, Spain.

External sources

- Instituto de Salud Carlos III. Subdirección General de Investigación Sanitaria, (01/A060), Spain.

INDEX TERMS

Medical Subject Headings (MeSH)

Diuretics [*therapeutic use]; Drinking; Hypercalciuria [complications] [diet therapy] [*drug therapy]; Kidney Calculi [etiology] [*prevention & control]; Randomized Controlled Trials as Topic; Thiazides [*therapeutic use]; Water [administration & dosage]

MeSH check words

Adult; Humans