Review

Calcium supplementation and kidney stone risk in osteoporosis: a systematic literature review

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ABSTRACT

Objectives. *This paper aims to examine the risk of nephrolithiasis in patients with osteoporosis and calcium supplementation.*

Methods. *This work is based on the systematic review of studies retrieved by a sensitive search strategy in Medline and Embase (1991–2010), and the Cochrane Central register of Controlled Trials (CENTRAL) up to 2010. The abstracts of the annual scientific meetings of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) (2008–2010) were also examined. The selection criteria were the following: patients with osteoporosis, on calcium supplementation alone or associated with other treatments for osteoporosis. We measured the likelihood of developing kidney stones, renal colic, changes in urinary sediment and serum parameters. We selected systematic literature reviews, randomised clinical trials (RCT) and cohort studies.*

Results. *We included 10 studies, 8 RCT and 2 cohort studies of moderate quality. All patients had osteoporosis (>8.000 patients), they were mostly women with a mean age of 50–70 years. Daily calcium doses varied from 120 mg up to 1.500 mg, and treatment duration from 3 days to 3 years. Changes in urinary sediment were found, but in general they were not clinically relevant. No cases of nephrolitiasis were found in more than a half of the included studies. In total there were 3 cases of kidney stone, 2 urinary tract calcifications, 16 cases of nephrolithiasis or urolithiasis, 4 of haematuria and 5 patients reporting kidney pain.*

Conclusion. *According to our results, calcium supplements in the treatment of osteoporosis alone or in combination with another type of treatment does not significantly increase the risk of nephrolithiasis or renal colic.*

Introduction

Osteoporosis is a disorder of bone characterised by reduced bone mass and increased fracture risk. Therapeutic regimens for osteoporosis include calcium supplementation, with or without vitamin D, alone or associated with other treatments (including calcitonin, raloxifene, biphosphonates, teriparatide, strontium ranelate, denosumab and so forth) (1-7).

The use of oral calcium supplementation for prevention and treatment of osteoporosis and osteopoenia is increasing. However, there is concern about the safety of calcium supplement, since it may cause hypercalciuria and may increase the risk of nephrolithiasis (8, 9).

Nephrolithiasis is a complex process, resulting from interactions among multiple factors. The increase in urinary calcium is not always associated with an increase in the risk of nephrolithiasis, if alterations in other relevant urinary constituents are in the opposite direction.

Recent studies, on the other hand, have shown that high dietary calcium intake or supplements are associated with a lower incidence of symptomatic stone disease (10). This beneficial effect is presumably due in part to an increased binding of calcium with oxalate in the intestine, leading to decreased oxalate absorption and excretion (11, 12). The decrease in urinary oxalate may compensate the effect of hypercalciuria on calcium oxalate stone formation. But, on the other hand, some studies (9) have reported an increased risk of calcium stone formation with oral calcium supplementation.

The aim of this study was, therefore, to systematically review the literature available on the use of calcium supplements in osteoporosis and the risk of nephrolithiasis. This information was afterwards examined and used by the experts of the Spanish Society of Rheu-

matology Consensus of osteoporosis to generate clinical practice recommendations for rheumatologists.

Methods

As a part of the Spanish Society of Rheumatology Consensus of osteoporosis, a systematic literature review was performed to address the experts' question on the use calcium supplements in osteoporosis and the risk of nephrolithiasis. A protocol of the review was established and further advice from the complete team of the Consensus was obtained.

Search strategy

The studies were identified by sensitive search strategies in the main bibliographic databases (Table I). For this purpose, an expert librarian collaborated and checked the search strategies.

The following bibliographic databases were screened as follows: Medline and Embase from 1991 to 20th July 2010, and the Cochrane Central register of Controlled Trials (CENTRAL) up to 20th July 2010. The abstracts of the annual scientific meetings of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) from 2008 to 2010 were also examined. There were no language limitations. All the retrieved references were managed in Endnote X.2. In the end, a hand search was completed by reviewing the references of the included studies, and all the publications or other information provided by the experts related to the systematic review were also examined.

Selection criteria

The studies retrieved by the above strategies were included if they met the following pre-established criteria. The patients studied had to be diagnosed of osteoporosis (all ages, both sexes, any cause), and they had to be taking oral calcium supplements (any kind of preparation) alone or associated with other treatments for osteoporosis. We measured the likelihood of having renal colic and oxalate or calcium phosphate kidney stones (whether or not it caused renal colic), the AP(CaOx) index, which is an index that measures the risk of developing kidney stones, changes in urinary sediment (uric calcium, phosphate, uric acid, oxalate uric pH), alkaline phosphatase (ALP) and other adverse events. We included in the search for systematic reviews randomised clinical trials (RCT) and cohort studies. We excluded articles on cancer or other disease other than osteoporosis, animal and basic science studies, and studies on calcitriol.

Screening of studies, data collection and analysis

Two reviewers (G. Candelas and J.A. Martinez-Lopez) screened the titles and abstracts of the retrieved articles for selection criteria independently. This process was done in 20-minute sessions. The two reviewers collected the data from the studies included by using *ad hoc* standard forms.

All collection was double by article and independent. Both reviewers entered the data from the forms into spreadsheets. If, while doing this, the reviewers found any discrepancy between them, then a consensus was reached by looking at the original article or by asking a third researcher (E. Loza). Articles that did not fulfil all the inclusion criteria or that had insufficient data were excluded.

To grade the quality, we used a modification of the Oxford Centre for Evidence-based Medicine Levels of Evidence in its May 2001 update (13) including the following: 1a) systematic reviews of RCT with homogeneity; 1b) individual RCT with narrow confidence intervals; 1c) trials in which all patients get harm or none does; 2a) systematic reviews of cohort studies with homogeneity; 2b) individual cohort study, or low quality randomised controlled trials; 2c) "outcomes" research and ecological studies; 3a) systematic reviews of case-control studies with homogeneity; 3b) individual case-control study; 4) case-series and poor quality cohort and case-control studies; and 5) expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles".

Evidence tables were produced. Meta-analysis was only planned in case enough homogeneity was present among the included studies.

We estimated the incidence rate (IR) of nephrolitiasis or urolithiasis (whether or not it caused renal colic) due to calcium supplementation per 1.000 patient-years, with 95% confidence intervals (95%CI) combining all studies.

Results

The result of the search strategies is presented in Table I by specific terms, and in total in Figure 1. We found 46 articles that were studied in detail because by title or abstract they seemed to be related to the study, or because they had no abstract to review. Table II shows the studies that were excluded after detailed review and the reasons for exclusion. Finally, 10 studies were included (Table III), of which 8 RCT (quality level 2a-b) and 2 cohort studies (quality level 2b-c), and their data retrieved. Table III shows the main characteristics of the included studies.

Related to the studies population, all patients had osteoporosis (>8.000 patients), mostly were women with mean ages around 50–70 years. Daily supplements intake of calcium varied from 120 mg up to 1.500 mg, and treatment duration from 3 days to 3 years. Most articles analysed different treatment strategies and all measured the abnormal serum and urinary markers of bone metabolism and registered nephrolithiasis cases. Using data from all the included studies, the incidence rate of nephrolitiasis or urolithiasis (whether or not it caused renal colic) due to calcium supplementation was 0.75 per 1.000 persons/year (95%CI 0.41–1.40).

Another author (quality level 2 b-c) (14) analysed the risk of nephrolithiasis with calcium supplements (625 mg/d) alone or associated with estrogen therapy. No significant changes were found in urinary calcium, oxalate, or citrate compared with baseline in any group. The urinary excretion of phosphate was significantly reduced in both groups, but the ratio calcium/citrate and AP (CaOx) did not change. There were no cases of nephrolithiasis.

In a double-blind placebo-controlled RCT (quality level 1c) (15), the effect of vitamin D 800 IU/d and calcium supplements 1.000 mg/d in combination or alone was analysed. No serious adverse

Table I. Search strategies in the different bibliographic databases and hits.

#	Strategy search and terms	Results
9	(#7) AND #8	194
8	((#4) OR #5) OR #6	3.422.381
7	((#1) AND #2) AND #3	460
6	"Review "[Publication Type] AND Review, Systematic OR Review, Multicase OR Review Literature OR Review, Academic OR Review of Reported Cases	1.533.210
5	((((("Cohort Studies"[Mesh] OR Cohort Study OR Studies, Cohort OR Study, Cohort OR Concurrent Studies OR Studies, Concurrent OR Concurrent Study OR Study, Concurrent OR Historical Cohort Studies OR Studies, Historical Cohort OR Cohort Studies, Historical OR Cohort Study, Historical OR Historical Cohort Study OR Study, Historical Cohort OR Analysis, Cohort OR Analyses, Cohort OR Cohort Analyses OR Cohort Analysis OR Closed Cohort Studies OR Cohort Studies, Closed OR Closed Cohort Study OR Cohort Study, Closed OR Study, Closed Cohort OR Studies, Closed Cohort OR Incidence Studies OR Incidence Study OR Studies, Incidence OR Study, Incidence)) OR ("Longitudinal Studies"[Mesh] OR Longitudinal Study OR Studies, Longitudinal OR Study, Longitudinal OR Longitudinal Survey OR Longitudinal Surveys OR Survey, Longitudinal OR Surveys, Longitudinal)) OR ("Follow-Up Studies"[Mesh] OR Follow Up Studies OR Follow-Up Study OR Studies, Follow-Up OR Study, Follow-Up OR Followup Studies OR Followup Study OR Studies, Followup OR Study, Followup)) OR ("Prospective Studies"[Mesh] OR Prospective Study OR Studies, Prospective OR Study, Prospective)	1.261.916
4	(((((((((("Clinical Trial "[Publication Type] OR "Clinical Trial, Phase I "[Publication Type]) OR Clinical Trial, Phase 1 OR "Clinical Trial, Phase II "[Publication Type]) AND Clinical Trial, Phase 2 OR "Clinical Trial, Phase III "[Publication Type]) OR Clinical Trial, Phase 3 OR "Clinical Trial, Phase IV "[Publication Type]) OR Clinical Trial, Phase 4 OR "Controlled Clinical Trial "[Publication Type]) OR "Multicenter Study "[Publication Type]) OR "Randomized Controlled Trial "[Publication Type])) OR (((((((("Clinical Trials as Topic"[Mesh] OR Clinical Trial as Topic)) OR ("Clinical Trials, Phase I as Topic"[Mesh] OR Clinical Trials, Phase I OR Phase 1 Clinical Trials OR Phase I Clinical Trials OR Clinical Trials, Phase 1 OR Evaluation Studies, FDA Phase I OR Evaluation Studies, FDA Phase 1 OR Microdosing Trials, Human OR Human Microdosing Trial OR Microdosing Trial, Human OR Trial, Human Microdosing OR Trials, Human Microdosing OR Human Microdosing Trials OR Drug Evaluation, FDA Phase I as Topic OR Drug Evaluation, FDA Phase I OR Drug Evaluation, FDA Phase 1)) OR ("Clinical Trials, Phase II as Topic"[Mesh] AND *Drug Evaluation, FDA Phase II as Topic OR Drug Evaluation, FDA Phase 2 as Topic OR Evaluation Studies, FDA Phase II as Topic OR Evaluation Studies, FDA Phase 2 as Topic)) OR ("Clinical Trials, Phase III as Topic"[Mesh] OR Clinical Trials, Phase 3 as Topic OR Evaluation Studies, FDA Phase III as Topic OR Drug Evaluation, FDA Phase III as Topic OR Drug Evaluation, FDA Phase 3 as Topic OR Evaluation Studies, FDA Phase 3 as Topic)) OR ("Clinical Trials, Phase IV as Topic"[Mesh] OR Clinical Trials, Phase 4 as Topic OR Drug Evaluation, FDA Phase IV as Topic OR Evaluation Studies, FDA Phase 4 as Topic OR Drug Evaluation, FDA Phase 4 as Topic OR Evaluation Studies, FDA Phase IV as Topic)) OR ("Randomized Controlled Trials as Topic"[Mesh] OR Controlled Clinical Trials, Randomized OR Clinical Trials, Randomized OR Trials, Randomized Clinical)) OR ("Multicenter Studies as Topic"[Mesh] OR Multicentre Studies as Topic OR Multicenter Trials OR Multicenter Trial OR Trial, Multicenter OR Trials, Multicenter OR Multicentre Trials OR Multicentre Trial OR Trial, Multicentre OR Trials, Multicentre))) OR ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms])	1.073.910
3	((((((((((("Kidney Calculi"[Mesh] OR Calculi, Kidney OR Calculus, Kidney OR Kidney Calculus OR Renal Calculi OR Calculi, Renal OR Calculus, Renal OR Renal Calculus OR Kidney Stones OR Kidney Stone OR Stone, Kidney OR Stones, Kidney)) OR ("Nephrolithiasis "[Mesh])) OR ("Urinary Calculi"[Mesh] OR Calculi, Urinary OR Calculus, Urinary OR Urinary Calculus OR Urinary Stones OR Stone, Urinary OR Stones, Urinary OR Urinary Stone OR Urinary Tract Stones OR Stone, Urinary Tract OR Stones, Urinary Tract OR Urinary Tract Stone)) OR ("Urolithiasis"[Mesh] OR Urinary Lithiasis OR Lithiasis, Urinary)) OR ("Ureteral Calculi"[Mesh] OR Calculi, Ureteral OR Calculus, Ureteral OR Ureteral Calculus))) OR ("Urinary Bladder Calculi"[Mesh] OR Bladder Calculi, Urinary OR Bladder Calculus, Urinary OR Calculi, Urinary Bladder OR Calculus, Urinary Bladder OR Urinary Bladder Calculus OR Bladder Stones OR Bladder Stone OR Stone, Bladder OR Stones, Bladder OR Calculi of Urinary Bladder OR Urinary Bladder Stones OR Bladder Stone, Urinary OR Bladder Stones, Urinary OR Stone, Urinary Bladder OR Stones, Urinary Bladder OR Urinary Bladder Stone OR Vesical Calculi OR Calculi, Vesical OR Calculus, Vesical OR Vesical Calculus OR Bladder Calculi OR Bladder Calculus OR Calculi, Bladder OR Calculus, Bladder OR Cystoliths OR Cystolith)) OR ("Ureterolithiasis"[Mesh] OR Ureterolithiases))) OR ("Renal Colic"[Mesh] OR Colic, Renal OR Colics, Renal OR Renal Colics OR Acute Renal Colic OR Acute Renal Colics OR Colic, Acute Renal OR Colics, Acute Renal OR Renal Colic, Acute OR Renal Colics, Acute OR Ureteral Colic OR Colic, Ureteral OR Colics, Ureteral OR Ureteral Colics)	36.706
2	((("Calcium"[Mesh] OR Coagulation Factor IV OR Factor IV, Coagulation OR Factor IV OR Blood Coagulation Factor IV)) OR ("Calcium Carbonate"[Mesh] OR Carbonate, Calcium OR Milk of Calcium OR Calcium Milk OR Vaterite OR Calcite OR Limestone OR Marble OR Chalk OR Aragonite)) OR ("Calcium, Dietary"[Mesh] OR Dietary Calcium)	440.597
1	(((((((("Osteoporosis"[Mesh] OR Osteoporoses OR Osteoporosis, Post-Traumatic OR Osteoporosis, Post Traumatic OR Post-Traumatic Osteoporoses OR Post-Traumatic Osteoporosis OR Osteoporosis, Senile OR Osteoporoses, Senile OR Senile Osteoporoses OR Senile Osteoporosis OR Osteoporosis, Age-Related OR Osteoporosis, Age Related OR Bone Loss, Age-Related OR Age-Related Bone Loss OR Age-Related Bone Losses OR Bone Loss, Age Related OR Bone Losses, Age-Related OR Age-Related Osteoporosis OR Age Related Osteoporosis OR Age-Related Osteoporoses OR Osteoporoses, Age-Related)) OR ("Osteoporosis, Postmenopausal"[Mesh] OR Perimenopausal Bone Loss OR Bone Loss, Postmenopausal OR Bone Losses, Postmenopausal OR Postmenopausal Bone Losses OR Osteoporosis, Post-Menopausal OR Osteoporoses, Post-Menopausal OR Osteoporosis, Post Menopausal OR Post-Menopausal Osteoporoses OR Post-Menopausal Osteoporosis OR Postmenopausal Osteoporosis OR Osteoporoses, Postmenopausal OR Postmenopausal Osteoporoses OR Bone Loss, Perimenopausal OR Bone Losses, Perimenopausal OR Perimenopausal Bone Losses OR Postmenopausal Bone Loss)) OR ("Female Athlete Triad Syndrome"[Mesh] OR Female Athlete Triad)) OR ("Decalcification, Pathologic"[Mesh] OR Decalcification, Pathological OR Pathological Decalcification OR Pathologic Decalcification OR Corticosteroid Induced Osteoporosis OR glucocorticoid induced osteoporosis OR Idiopathic Osteoporosis OR Involutional Osteoporosis OR Juvenile Osteoporosis OR Primary Osteoporosis OR Secondary Osteoporosis OR Bone Fragility Endocrine Osteoporosis OR Osteoporotic Decalcification)) OR ("Bone Density"[Mesh] OR Bone Densities OR Density, Bone OR Bone Mineral Density OR Bone Mineral Densities OR Density, Bone Mineral OR Bone Mineral Content OR Bone Mineral Contents OR BMD)) OR ("Fractures, Bone"[Mesh] OR Broken Bones OR Bone, Broken OR Bones, Broken OR Broken Bone OR Bone Fractures OR Bone Fracture OR Fracture, Bone)) OR ((((((((((((Bone mineral density[All Fields])) OR (low bone mass)) OR (low bone mass density)) OR (low bone mineral density)) OR (low bone mass in premenopausal women with depression)) OR (low bone mass premenopausal women)) OR (low bone)) OR (low bone density)) OR (postmenopausal bone loss)) OR (bone loss osteoporosis)) OR (bone loss postmenopausal)) OR (bone loss))	280.220

events were registered but 4 cases of nephrolithiasis.

A RCT (quality level 2b-c) (16) analysed 4 treatments: cyclic estrogen/progestogen therapy (group 1), calcium supplements 2.000 mg/d (group 2), intermittent cyclic etidronate therapy (group 3), and an ADFR treatment with triiodothyronine as activator and etidronate as depressor (group 4). In group 1, 3 calcium supplements 120 mg/d were added. ALP and the excretion of hydroxyproline decreased in groups 1 and 3. There were no cases of nephrolithiasis.

Furthermore, in a 1-year open RCT (quality level 2a-b) (17) the effect of intermittent administration of 200 IU intranasal calcitonin plus vitamin D and calcium supplements *vs*. vitamin D and calcium supplements were examined. Urinary Ca/creatinine and pyrilinks-D/creatinine levels and serum intact parathormone (iPTH) and ALP levels were significantly decreased from baseline in the calcitonin group. There were no cases of nephrolitiasis.

Kurland *et al*. (18) examined in a double-blind placebo-controlled RCT (quality level 1c) the effect of iPTH plus 1.500 mg/d of calcium (dietary and supplements) and 400 IU/d of vitamin D. There were no significant changes in serum calcium concentrations, urinary calcium or 1–25 dihydroxyvitamin D in either group. All markers of bone turnover increased in the PTH-group, especially the osteocalcin and urinary N-telopeptide.

In a prospective study (quality level 2b) (19) men with osteoporosis and hypercalciuria who had been treated with thiazides or calcium supplements plus vitamin D were analysed. Urinary calcium excretion significantly fell in the thiazide group. There were no cases of nephrolithiasis.

We included a 2-parallel double-blind placebo-controlled RCT (quality level 1c) (20). In study 1, 1.637 women with osteoporosis were included, while in study 2, 2.437 men with osteoporosis were included. All of them took 1.000 mg/d of oral calcium supplements and vitamin D 400–1200 IU/d, and were randomised to teriparatide (TPTD) 20 μgr/d, 40 μgr/d or placebo. In all groups urinary calcium excretion significantly

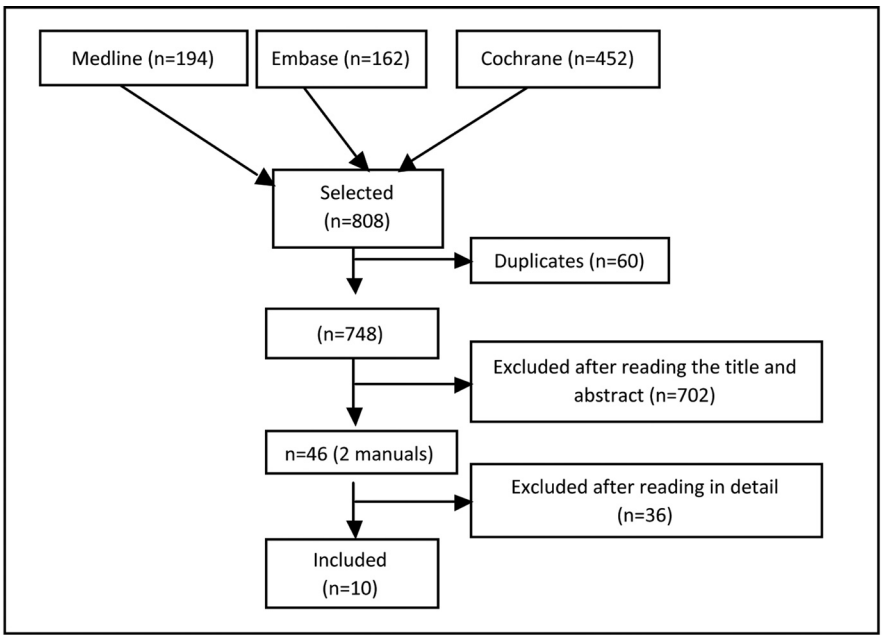

Fig. 1. Articles retrieved by the different search strategies and result of selection and appraisal process.

Table II. Excluded studies and reasons for exclusion.

Study	Reason for exclusion
Aloia (1998) (24)	Treatment with calcitriol
Alexandersen (2001) (32)	Data of urinary calcium or nephrolithiasis not shown
Agnusdei (1992) (33)	Data of urinary calcium or nephrolithiasis not shown
Agnusdei (1997) (34)	Data of urinary calcium or nephrolithiasis not shown
Bonnick (2007) (35)	Data of urinary calcium or nephrolithiasis not shown
Braga de Castro (1999) (36)	Data of urinary calcium or nephrolithiasis not shown
Bravenboer (1999) (37)	Data of urinary calcium or nephrolithiasis not shown
Bunout (2006) (38)	Data of urinary calcium or nephrolithiasis not shown
Cascella (2005) (39)	Data of urinary calcium or nephrolithiasis not shown
Chailurkit (2003) (40)	Data of urinary calcium or nephrolithiasis not shown
Chesnut (1995) (41)	Data of urinary calcium or nephrolithiasis not shown
Crhistiansen (1990) (42)	Data of urinary calcium or nephrolithiasis not shown
Delmas (2006) (43)	Data of urinary calcium or nephrolithiasis not shown
Domrongkitchaiporn (2000) (26)	Treatment with calcitriol
Gallagher (1990) (27)	Treatment with calcitriol
Gennari (1989) (44)	Unrecovered article
Homik (1998) (45)	Data of urinary calcium or nephrolithiasis not shown
Horowitz (1984) (46)	Very poor quality
Lee (2006) (47)	Unrecovered article
Orimo (1994) (48)	Data of urinary calcium or nephrolithiasis not shown
Ott (1989) (25)	Treatment with calcitriol
Overgaard (1991) (49)	Data of urinary calcium or nephrolithiasis not shown
Parviainen (1999) (50)	Data of urinary calcium or nephrolithiasis not shown
Reginster (2003) (51)	Data of urinary calcium or nephrolithiasis not shown
Resch (1989) (52)	Data of urinary calcium or nephrolithiasis not shown
Ringe (1991) (53)	Editorial
Rossini (2000) (54)	Data of urinary calcium or nephrolithiasis not shown
Ryan (2000) (55)	Data of urinary calcium or nephrolithiasis not shown
Sethi (2008) (56)	Data of urinary calcium or nephrolithiasis not shown
Shiraki (2003) (57)	Data of urinary calcium or nephrolithiasis not shown
Tekeoglu (2005) (58)	Data of urinary calcium or nephrolithiasis not shown
Thamsborg (1996) (59)	Data of urinary calcium or nephrolithiasis not shown
Tilyard (1990) (60)	Unrecovered article
Trovas (2002) (61)	Data of urinary calcium or nephrolithiasis not shown
Zegels (2001) (62)	Data of urinary calcium or nephrolithiasis not shown
Anonymous (2007) (63)	Editorial

Table III. Main characteristics of the included studies.

Study	Population	Intervention	Outcomes	Quality*/comments
Domrongkitchaiporn (14), 2002 RCT, 3 m follow-up	n=61 (n=31 calcium + estrogen therapy, mean age: 54 yr; n=30 calcium, mean age: 66 yr) IC: PM women with OP EC: prior use of drugs affecting bone metabolism	• Calcium suppl 625 mg/d + conjugated equine estrogen 0.625 mg/d and 5 mg medrogestone acetate/d from day 1 to 12 of each month • Calcium 625 mg/d	• Urinary excretion of calcium, oxalate, citrate, phosphate • Calcium/citrate ratio • AP(CaOx) index • Nephrolithiasis	• Oxford 2b-c
Grant (15), 2005 double-blind placebo control RCT, 2 yr follow-up	n=5.292 (n=1.306 vit D + calcium suppl; n=1.343 vit D; n=1.311 calcium suppl; n=1.332 palcebo), mean age 77 yr, 85% women IC: ≥70 yr with OP fracture within 10 yr EC: bed or chair bound, cognitive impairment, cancer, renal stone, daily intake ≥200 IU vitamin D or ≥500 mg calcium supplements; intake in the past 5 years of bisphosphonates, calcitonin, hormonereplacement therapy	• Vit D 800 UI/d • Calcium suppl 1.000 mg/d • Vit D 800 UI/d + calcium 1.000 mg/d • Placebo	• Serum calcium • Nephrolithiasis	• Oxford 1c
Hasling (16), 1994 RCT, 3 yr follow-up	n=74: cyclic oestrogen/progestogen therapy (group 1, n=20), calcium suppl (group 2, n=17), intermittent cyclic etidronate therapy (group 3, n=19), ADFR treatment with T3 as activator and etidronate as depressor (group 4, n=18) CI: PM women (52–75 yr) with spinal crush fracture OP CE: treatments that alter bone or calcium metabolism, alcohol abuse, thyroid disorders, abnormalities of renal or hepatic function prior treatment for OP	• Estrogen + progestogen: 2 mg estradiol/1 mg estriol 1/d x 12 d → 2 mg estradiol/1 mg estriol /1 mg norethisteronacetate 1/d days 13-22 → 1mg estradiol/0.5 mg estriol 1/d from day 23 to 28 + calcium suppl 120 mg/d • Calcium suppl 2.000 mg/d • Etidronate 400 mg x 2 w → 13 w etidronate free (10 cycles) + calcium suppl 120 mg/d • ADFR (cycles): 50 µgr T3 2/d x 1 w + etidronate 400 mg 2v/d x 2 w → 13 w etidronate free + calcium suppl 120 mg/d	• Urinary calcium • ALP • Hidroxiproline excretion • Nephrolithiasis	• Oxford 2b-c • 29 dropouts (6 group 1; 8 group 2; 3 group 3; 12 group 4)
Kaskani (17), 2005 Open RCT, 1 yr follow-up	n=102 (n=57 calcitonin + vit D + calcium suppl, mean age 59 yr; n=45 vit D + calcium suppl, mean age 58 yr) IC: PM women (51–70 yr) without any kind of medication that could affect bone metabolism for at least 6 m before EC: secondary OP, kidney or hepatic insufficiency, cancer, hematological diseases, thyroid diseases, treatment with thyroxin, chronic diseases that affect bone metabolism	• Calcitonin 200 IU/d intranasal 1 m on-1 m off + vit D 0.25 µgr/d + calcium suppl 500 mg/d • Vit D 0.25 µgr/d + calcium suppl 500 mg/d	• Urinary calcium • ALP • Ca/creatinine ratio • Pyrilinks-D/creatinine ratio • iPTH	• Oxford 2a-b • 11 dropouts (7 calcitonin group; 4 in vit D +calcium group)
Kurland (18), 2000 double-blind placebo control RCT, 18 m follow-up	n=23 (n=10 iPTH + vit D + calcium, mean age 54 yr; n=13 placebo, mean age 49 yr) IC: men (30–60 yr) and idiopatic OP (z-score <-2.0 or a T-score <-2.5 at the lumbar spine or femoral neck) EC: OP drugs in the previous 6 m	• iPTH 400 UI/d sc + vit D 400 UI/d + calcium dietary and suppl 1.500 mg/d • Placebo	• Urinary calcium • Serum calcium • 1-25 dihidroxivitamine D • Osteocalcin • Urinary N-telopéptido	• Oxford 1c
Legroux-Gerot (19) , 2004 Prospective study, 18 m follow-up	n=27 (n=14 hydrochlorothiazide, mean age 53 yr; n=13 calcium suppl + vit D, mean age 48 yr) IC: hypercalciuretic osteoporotic male patients	• Hydrochlorothiazide 44 mg ± 9 mg/d • Calcium suppl 1.100mg ± 251 mg/d + vit D 1.277 UI ± 685 IU/d	• Urinary calcium • Nephrolithiasis	• Oxford 2b
Miller (20), 2007 2 parallel double-blind placebo-controlled RCT 1 yr follow-up	Study 1: n=1.637 PM women, mean age 69 yr Study 2: n=437 men, mean age 58 yr IC: OP patients or patients with low bone mass EC: nephrolithiasis or urolithiasis, impaired hepatic or renal function, diseases or drugs that alter bone metabolism in the previous 2–24 m	• TPTD 20 µg/d sc + calcium suppl 1.000 mg/d + vit D 400–1.200 UI/d • TPTD 40 µg/d sc + calcium suppl 1.000 mg/d + vit D 400–1.200 UI/d • Placebo	• Urinary calcium • Neprholithiasis	• Oxford 1c • 7 dropouts (4 women y 1 man in TPTD 20 µg group; 1 woman in TPTD 40 µg group, 2 women in the placebo group)
Need (21),1991 RCT, 3 d follow-up	n=35 women mean age 68 yr IC: hospitalised PM women with OP	• Calcium suppl 1.000 mg/d (effervescent) • Calcium suppl 1.000 mg/d (carbonate) • Calcium suppl 1.200 mg/d (carbonate)	• Urinary calcium • Urinary hidroxiproline	• Oxford 3b
Recker (22), 1996 double-blind placebo control RCT, 1 yr follw-up	n=197 (n=94 prevalent fractures, mean age 75 yr; n=103 non prevalent fractures, mean age 72 yr) IC: women >60 yr living independently and consuming <1 g/day of calcium	• Calcium suppl 1.200 mg/d • Placebo	• Neprholithiasis	• Oxford 2c
Yasui (23), 2009 prospective cohort, 3 m follow-up	n=12, mean age: 63 yr IC: PM women with OP and had stones comprised of calcium phosphate, calcium oxalate or both EC: prior treatments for OP, primary hyperparathyroidism, renal tubular acidosis or other metabolic conditions associated with urinary tract infections or renal failure	• Alendronate 5 mg/d	• Urinary calcium • Urinary oxalate • Urinary phosphate • AP(CaP) index • AP(CaOx) index • Nephrolithiasis	• Oxford 2b

*Quality was assessed according to the modification of the Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009 Update).
RCT: randomised controlled trial; IC: inclusion criteria; EC: exclusion criteria; OP: osteoporosis; PM: postmenopausal; suppl: supplement; vit: vitamin; yr: year; m: moth; w: week; d: day; mg:milligram; µgr: microgram; Ca: calcium; AP(CaOx): ion activity product of calcium oxalate salts in urine; sc: subcutaneous; T3: triiodothyronine; ADFR: activate, depress, free, repeat; GC: glucocorticoids; ALP: alkaline phosphatase; iPTH: intact parathormone; PTH: parathormone; TPTD: teriparatide; BMD: bone mineral density; RA: rheumatoid arthritis.

increased. Hypercalciuria cases were not clinically relevant. In study 1, 2women in each of the placebo and TPTD 20 groups had a kidney stone, 1 in each TPTD group had urinary tract calcifications. Kidney pain and urolithiasis was reported by 3 women in the TPTD 20 and by 1 in the 40 group. Two in the placebo, 6 in the TPTD 20, and 2 in the 40 group had urolithiasis. Six in the placebo group and 4 in each of the TPTD groups reported haematuria. In study 2, 5 men had possible urolithiasis. One in the placebo, 2 in the TPTD 20, and 1 in the TPTD 40 group had a kidney calculus. One man in the TPTD 40 group reported kidney pain.

Need *et al*. (21) performed a RCT (quality level 3b), in which 3 calcium supplements preparations (1.000 mg/d effervescent, 1.000 mg/d carbonate, 1.200 mg/ carbonate) were examined. Urinary calcium increased significantly in all groups without significant differences between them. The decrease of urinary hydroxyproline levels in the end returned to baseline levels.

We selected a double-blind, placebo-control RCT (quality level 2c) (22) in which calcium supplements 1.200 mg/d were provided. There were no cases of nephrolithiasis.

In a prospective study (quality level 2b) (23), 12 women were treated with alendronate 5 mg/d and calcium supplements for 3 months. The rate AP(CaP) index was significantly reduced, but urinary calcium, oxalate, phosphate and the AP(CaOx) index did not significantly change. There were no cases of nephrolithiasis.

Discussion

In the present study, we have analysed the possibility of developing urinary sediment changes, nephrolithiasis and renal colic with the use of oral calcium supplementation, alone or in combination with other drugs in patients with osteoporosis. For the purpose of the present systematic literature review, we decided to include RCT and cohort controlled studies. We considered this as the most appropriate way to answer the research question.

We finally included a total of 10 studies (14-23); all were RCT except for 2 prospective cohort studies (19, 23). The quality of most of them was moderate. These studies analysed more than 8.000 patients with osteoporosis, mostly middle aged women. All received treatment with oral calcium supplements and some dietary calcium as well and the majority bisphosphonates or other osteoporosis treatments. Besides, there was a great variability in daily calcium doses and treatments duration. Interestingly, only in 4 of the included studies, the urinary sediment changes or nephrolithiasis were the main outcomes.

Regarding urinary sediment and serum, although changes were found, generally they were not clinically relevant and were probably related to the effect of other drugs rather than to calcium supplementation. Changes included urinary calcium or phosphate, Ca/creatinine and pyrilinks-D/creatinine level decrease (14, 19, 20), urinary calcium increase (21), hypercalcemia (20), and decrease levels of serum ALP and iPTH or the excretion of hydroxyproline (16, 17). But, on the other hand, there were no significant changes in urine calcium, oxalate, or citrate and serum calcium and vitamin D levels in many studies (14, 17, 18, 23).

Moreover, we found patients with kidney stone or nephrolitiasis, but taking into account the total number of patients analysed in this study the incidence of these outcomes is low. In fact, no cases of nephrolitiasis were found in more than a half of the included studies (14, 16, 17, 19, 22). There were three cases of kidney stone (20), two urinary tract calcifications (20), sixteen cases of nephrolithiasis or urolithiasis, four of haematuria and five reporting kidney pain (15, 20). Besides, the AP (CaOx) index, which is an index that measures the risk of developing kidney stones, did not significantly change in those studies in which it was analysed (14, 23). However, due to the great variability regarding the study designs, follow-up periods and outcomes, these results should be considered carefully.

It has been suggested that stone risk is higher in osteoporosis patients taking bisphosphonates (10). Bisphosphonates, by increasing parathyroid hormone secretion, tend to improve calcium absorption, and at the same time they down-regulate bone remodelling. The first effect would lead directly to increased absorptive calcemia, and with the latter, absorptive calcemia would be exaggerated because of decreased ability to damp calcemic oscillations. As a result, absorptive calciuria would be predicted to be greater with the bisphosphonate. But on the other hand, other studies suggest a potential benefit by reducing the risk of renal stone formation (28, 29). In addition, it has been published that urinary calcium excretion was increased with TPTD treatment, but the authors considered that the magnitude of these changes were unlikely to be clinically relevant or warrant urinary calcium monitoring for most patients (20). Other papers have shown that estrogen therapy increases the risk of nephrolithiasis at least in healthy postmenopausal women (30), as well as calcitonin (31). Unfortunately, our study could not confirm any of these statements.

But in this context, one of the main limitations of the present study was related to the selected outcome. As exposed before, we searched for studies which reported changes in urinary sediment and/or kidney stones (symptomatic or not). In the literature, there are many high quality RCT in osteoporosis. However, many of them do not consider them as a potential adverse event, mainly because all of them are focused on the effect and safety of bisphosphonates rather than on calcium supplements. Moreover, even in those in which it is reported, these outcomes are shown as secondary in the results section, but not in the abstract, mesh terms or key words. As a consequence, this kind of studies is hard to capture in a systematic literature. Thus, we conducted a sensible search strategy and performed an extensive hand review. It would therefore be advisable to conduct further studies to draw more accurate and reliable conclusions in this context.

In addition, in a well designed RCT, it was shown that calcium supplements were associated with renal calculi, but this trial was performed in postmenopausal women, in which it was not clear if they had or not osteoporosis. Therefore, this kind of study was not selected.

In summary, the available evidence does not support a causal linkage between nephrolithiasis risk and calcium supplementation intake (alone or in combination with another type of treatment) of a magnitude likely to be encountered in osteoporosis patients (level of evidence 2b, grade B recommendation).

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