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Calcium supplementation on bone loss in postmenopausal women

[Review]

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Outline

Graphics

Abstract

Background: Although calcium is one the simplest and least expensive strategies for preventing osteoporotic fractures calcium supplementation is nevertheless not without controversy (Kanis 1989; Nordin 1990). The Food and Drug Administration in the US has permitted a bone health claim for calcium-rich foods, and the NIH in its Consensus Development Process approved a statement that high calcium intake reduces the risk of osteoporosis.

Objectives: To assess the effects of calcium on bone density and fractures in postmenopausal women.

Search strategy: We searched Cochrane Controlled Register, MEDLINE and EMBASE up to 2001, and examined citations of relevant articles and proceedings of international meetings.

Selection criteria: Trials that randomized postmenopausal women to calcium supplementation or usual calcium intake in the diet and reported bone mineral density of the total body, vertebral spine, hip, or forearm or recorded the number of fractures, and followed patients for at least one year were considered for inclusion.

Data collection and analysis: Three independent reviewers assessed the methodologic quality and extracted data for each trial. For each bone density site (lumbar spine, total body, combined hip and combined forearm), we calculated the weighted mean difference in bone density between treatment and control groups using the percentage change from baseline. We constructed regression models in which the independent variables were year and dose, and the dependent variable was the effect size. This regression was used to determine the years across which pooling was appropriate. Heterogeneity was asssesed. For each fracture analysis we calculated a risk ratio.

Main results: Fifteen trials, representing 1806 participants, were included. Calcium was more effective than placebo in reducing rates of bone loss after two or more years of treatment. The pooled difference in percentage change from baseline was 2.05% (95% CI 0.24 to 3.86) for total body bone density, 1.66% (95% CI 0.92 to 2.39) for the lumbar spine at 2 years, 1.60% (95% CI 0.78 to 2.41) for the hip, and 1.91% (95% CI 0.33 to 3.50) for the distal radius. The relative risk of fractures of the vertebrae was 0.79 (95% CI 0.54 to 1.09); the relative risk for non-vertebral fractures was 0.86 (95% CI 0.43 to 1.72).

Conclusions: Calcium supplementation alone has a small positive effect on bone density. The data show a trend toward reduction in vertebral fractures, but it is unclear if calcium reduces the incidence of non vertebral fractures.

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Background

Of all the available preventive strategies for osteoporotic fractures, calcium is the simplest and least expensive. An essential nutrient with minimal toxicity, calcium supplementation is nevertheless not without controversy (Kanis 1989; Nordin 1990). The Food and Drug Administration in the US has permitted a bone health claim for calcium-rich foods, and the NIH in its Consensus Development Process approved a statement that high calcium intake reduce the risk of osteoporosis.

Cumming et al recently reviewed both observational and controlled clinical trials relating calcium intake to fracture incidence (Cumming 1997). Observational studies often provide biased estimates and the authors did not find conclusive evidence of benefit from the controlled trials alone. Furthermore, they did not examine the effect of calcium supplementation on bone mineral density (Cumming 1997). Mackerras and Lumley conducted a meta-analysis of randomised controlled trials (RCTs) examining the effect of increasing calcium ingestion on bone density in women (Mackerras 1997), but their analysis omitted four of the 15 available studies, failed to contact authors to obtain missing data and clarify data report accuracy, and did not address the effect on fractures. We have therefore conducted a systematic review to quantify the effect of calcium supplementation on postmenopausal bone loss and fractures.

Objectives

To summarize controlled trials examining the effect of calcium on bone density and fractures in postmenopausal women.

Criteria for considering studies for this review

Types of participants

RCTs of calcium supplementation in women older than 45 years with absence of menses for a minimum of six months.

Types of intervention

Treatment with doses of calcium at least 400 mg/day. We also included RCTs in which both active and control groups received a maintenance dose of vitamin D providing the loading dose was no more than 300,000 IU, and the maintenance dose was no more that 400 IU per day (Chevalley 1994; Aloia 1994).

Types of outcome measures

1) Bone density sites included lumbar spine, total body, combined hip and combined forearm
2) Fractures

Types of studies

We developed and published an a priori protocol according to the methods recommended by the Cochrane Collaboration (Mulrow 1997; Oxman 2002).

Search strategy for identification of studies

To identify RCTs of calcium supplementation, we evaluated the Cochrane Controlled Trials Register (CCTR) up to 2001 (Dickersin 1994) and MEDLINE and EMBASE from January 1966 to April 2001 including Current Contents of the six months prior to April 2001. We also conducted hand searches of bibliographic reference. We asked content experts to identify published or unpublished relevant RCTs we had overlooked. Two reviewers (JP, BS) examined each title generated from the search and identified potentially eligible articles for which we obtained the abstracts. For abstracts consistent with study eligibility, we obtained the full article text.

1. osteoporosis, postmenopausal/
2. osteoporosis/
3. osteoporosis.tw.
4. exp bone density/
5. bone loss$.tw.
6. (bone adj2 densit$).tw.

7. or/2-6
8. menopause/
9. post-menopaus$.tw.
10. postmenopaus$.tw.
11. or/8-10
12. 7 and 11
13. 1 or 12
14. calcium/
15. calcium carbonate/
16. calcium, dietary/
17. (calcite or calcium).tw.
18. or/14-17
19. 13 and 18
20. meta-analysis.pt,sh.
21. (meta-anal: or metaanal:).tw.
22. (quantitativ: review: or quantitativ: overview:).tw.
23. (methodologic: review: or methodologic: overview:).tw.
24. (systematic: review: or systematic: overview).tw.
25. review.pt. and medline.tw.
26. or/20-25
27. 19 and 26
28. clinical trial.pt.
29. randomized controlled trial.pt.
30. tu.fs.
31. dt.fs.
32. random$.tw.
33. (double adj blind$).tw.
34. placebo$.tw.
35. or/28-34
36. 19 and 35

Methods of the review

Statistical analysis:

For each bone density site (lumbar spine, total body, combined hip and combined forearm), we calculated the weighted mean difference in bone density between treatment and control groups using the percentage change from baseline in the treatment and placebo groups and the associated SDs. We constructed regression models in which the independent variables were year and dose, and the dependent variable was the effect size. We used this regression to determine the years across which pooling was appropriate. To assess if the magnitude of heterogeneity (differences in apparent treatment effect across studies) was greater than one might expect by chance, we conducted a test based on the chi square distribution with N-1 degrees of freedom where N is the number of studies (Fleiss 1993). For each fracture analysis we calculated a risk ratio (a relative risk) using methods described by Fleiss (Fleiss 1993). We derived risk ratios by constructing two by two tables for vertebral and non-vertebral fractures. We tested for heterogeneity using a chi-square procedure (Hedges 1985).

A Priori Hypotheses Regarding Heterogeneity:

To explore reasons for large differences in results between studies (heterogeneity) we developed a priori hypotheses relating to the methodological quality of the study, and the study population. Specifically, we compared results in RCTs grouped in the following ways:
i) different methodological quality (randomization concealed or unconcealed; blinded or unblinded; extent of loss to follow-up);
ii) different doses of calcium supplementation (above and below 800 mg/day, a value that approximates the median dose of calcium supplementation in the eligible trials);
iii) type of calcium formulation (a manuscript reviewer suggested this hypothesis);
iv) early postmenopausal women (< 5 years) and late postmenopausal women (> 5 years);
v) different levels of baseline calcium intake (less than or greater than 750 mg., a value that approximates the median baseline intake in the eligible trials); and
vi) for forearm and hip bone density, subregion of measurement.

We tested whether our a priori hypotheses could explain variability in the magnitude of treatment effects across studies using a procedure described by Hedges and Olkin (Hedges 1985). To test for publication bias, we constructed plots of the relationship between sample size and the magnitude of the treatment effect.

Grading the strength of the evidence
The common system of grading the strength of scientific evidence for a therapeutic agent that is described in the CMSG module scope and in the Evidence-based Rheumatology BMJ book (Tugwell 2003) was used to rank the evidence included in this systemtic review. Four categories are used to rank the evidence from research studies: Platinum, Gold, Silver, and Bronze. The ranking is included in the synopsis of this review.

Description of the studies

Electronic and hand searching uncovered a total of 66 published papers that addressed the relationship between calcium intake and bone mineral density. Twenty three described RCTs (Aloia 1994; Chapuy 1992; Chevalley 1994; Dawson-Hughes 1997; Dawson-Hughes 1990; Elders 1991; Hansson 1987; Lamke 1978; Lau 1992; Nelson 1991; Orwell 1990; Polley 1987; Prince 1991; Prince 1995; Recker 1977; Recker 1985; Recker 1996; Reid 1993; Riggs 1998; Riis 1987; Smith 1981; Strause 1994), of which seven were excluded for various reasons including combination with Vitamin D (Chapuy 1992; Dawson-Hughes 1997), male participants (Orwell 1990), trial duration less than one year (Lau 1992; Polley 1987) or measurement of bone density exclusively at the ultra-distal forearm site (Recker 1977; Recker 1985).

Of the 16 authors of eligible studies whom we contacted for missing data, 13 provided us with additional data (Aloia 1994; Chevalley 1994; Dawson-Hughes 1990; Lamke 1978; Nelson 1991; Prince 1991; Prince 1995; Recker 1996; Reid 1993; Riggs 1998; Riis 1987; Smith 1989; Strause 1994). Two investigators were unable to provide data (Hansson 1987; Smith 1981), of which one had to be excluded from the analysis due to lack of the information (variance) of the reported data (Smith 1981). We were unable to contact one investigator (Elders 1991) though the study provided sufficient data for inclusion. Thus, 15 RCTs both fulfilled our eligibility criteria and provided useful data for pooling (Aloia 1994; Chevalley 1994; Dawson-Hughes 1990; Elders 1991; Hansson 1987; Lamke 1978; Nelson 1991; Prince 1991; Prince 1995; Recker 1996; Reid 1993; Riggs 1998; Riis 1987; Smith 1989; Strause 1994). Of the 13 investigators who did provide additional data, 11 were able to provide us with all the information

we sought (Aloia 1994; Chevalley 1994; Dawson-Hughes 1990; Lamke 1978; Prince 1991; Prince 1995; Recker 1996; Reid 1993; Riggs 1998; Smith 1989; Strause 1994), while the other two provided us with some of the information we requested (Nelson 1991; Riis 1987).

The 15 RCTs included 1806 patients, of whom 953 patients received calcium supplementation. Table 1 summarizes the characteristics of these studies. Of the 15 studies, 13 investigators confirmed that the randomization was concealed (Aloia 1994; Chevalley 1994; Dawson-Hughes 1990; Lamke 1978; Nelson 1991; Prince 1991; Prince 1995; Recker 1996; Reid 1993; Riggs 1998; Riis 1987; Smith 1989; Strause 1994). Thirteen investigators confirmed that patients, caregivers and those measuring outcome were blind to allocation (Aloia 1994; Chevalley 1994; Dawson-Hughes 1990; Lamke 1978; Nelson 1991; Prince 1991; Prince 1995; Recker 1996; Reid 1993; Riggs 1998; Riis 1987; Smith 1989; Strause 1994). None of the trials had between 1% and less than 5% loss to follow-up, 13 trials had a loss to follow-up between 5% and 20%, and two trials lost more that 20% of their patients. We were unable to obtain the methodology information for two of the trials (Elders 1991; Hansson 1987).

Methodological qualities of included studies

Three reviewers (JP, NK, BS) rated the methodologic quality of each eligible study with respect to whether patients, care givers, and those measuring outcome are blind to allocation, and the extent of loss to follow-up.

We used more than one reviewer in the selection of studies, the assessment of methodologic quality and the extraction of data. For all aspects of the review in which raters made duplicate judgements, they resolved disagreements by consensus. The inter-observer agreement measured for the quality assessment with kappa (Landis 1977) for blinding of patients, caregivers, and those assessing outcome was 0.85, and for duration of follow-up was 0.49.

Results

Fractures:

Five studies including 576 women reported fractures as an outcome (Chevalley 1994; Hansson 1987; Recker 1996; Reid 1993; Riggs 1998). All five trials investigated the influence of calcium supplementation on vertebral fractures. The pooled RR indicated a non-significant trend toward reduction in vertebral fractures in the calcium group (RR 0.79, 95%CI 0.55 to 1.13, p = 0.2). The two trials (Chevalley 1994; Riggs 1998) that reported non-vertebral fractures had very few events, and the confidence interval on the pooled estimate is therefore very wide (RR 0.86, 95% CI 0.43 to 1.72, p = 0.66). For both vertebral and non-vertebral fractures, the effect of calcium was consistent across trials (heterogeneity p = 0.40, 0.54 respectively) (Table 02).

Bone Mineral Density:

Table 3 summarizes the impact of calcium on bone mineral density at the four sites we examined. Our initial analyses suggested that we could pool across years in all instances but one, the lumbar spine. Here, the estimated effect of calcium for years three and four was actually less than for years one and two (Table 03). For all sites but lumbar spine at three to four years of follow-up, calcium showed an effect of between 1.6 and just over 2% in bone density. At all sites, we found considerable variability in estimates

of effect across trials reflected in statistically significant tests of heterogeneity.
Our search for explanations of this heterogeneity proved largely fruitless (Table 04). For the total body measurement, we observed a statistically significantly greater effect in primary than secondary studies, and with smaller doses of calcium than larger doses. For lumbar spine at two years, the effect was in the opposite direction, suggesting a larger impact of higher doses.

We did find an apparently greater effect of calcium carbonate than calcium citrate on total body bone density and on the hip site (Table 05). However, the trend for the lumbar spine measurements was in the opposite direction (larger effects with calcium citrate). Moreover, the total body and hip site analyses were based on only a single RCT using calcium citrate and two RCTs using calcium carbonate. Thus, any interferences based on this analysis are extremely weak. No other subgroup analysis showed statistically significant results.

Discussion

This systematic review is restricted to calcium supplementation with minimal vitamin D. Large studies of Vitamin D have shown conflicting results (Chapuy 1992; Dawson-Hughes 1997). We summarize the data from all randomized trials of Vitamin D in another meta-analysis in this series.

Our data suggest a relatively small, but possibly important effect of calcium supplementation on bone density in postmenopausal women. The inference that calcium increases bone density is strengthened by the consistency of the finding across four sites of measurement (Table 3). The inference is, however, weakened by the large loss to follow-up in most studies (Table 1) and by the unexplained heterogeneity of results across studies (Tables 3 and 4).

To establish the effect of calcium supplementation on fractures would require large, relatively long trials measuring fracture incidence. We found only five RCTs that measured fracture rate. The point estimate from the meta-analysis of these five studies suggested a potentially important reduction in vertebral fractures (RR 0.79, 95%CI 0.55 to 1.13, p = 0.14) (relative risk 0.79), and a smaller reduction in risk of non-vertebral fractures (RR 0.86, 95% CI 0.43 to 1.72, p = 0.66). Thus, even for vertebral fractures, a true underlying substantial reduction in the relative risk of fractures (46%) or small increase in the relative risk of fractures (10%) both remain plausible.

The estimates provided by our analysis are limited by problems inherent in the original studies, including a lack of uniformity in outcome measures. In 1996, during the Conference on Outcome Measures in Rheumatology Clinical Trials (OMERACT 3), participants agreed on a potential core set of outcome measures for osteoporosis (Cranney 1997). A core set will permit the comparison of data across all trials to perform accurate meta-analyses. The primary outcomes will be the number of women experiencing new non-vertebral and vertebral fractures (clinical and radiographic), bone mineral density and toxicity (measured by withdrawals and side effects), as recommended by the OMERACT group in 1997 (Cranney 1997).

As well as considering these issues, future investigations should take care with the selection of study

patients, the dose and formulation of calcium administration, and the measures of outcome. When they select study populations, investigators should also consider factors that may influence the effectiveness of calcium supplementation, including age, years since menopause, dietary calcium intake, and vitamin D status. Site of bone density measurement, type and precision of the instruments, and definition of fracture may also influence the apparent magnitude of treatment effects.

In summary, we found small but statistically significant and potentially important effects of calcium supplementation in bone loss over a two-year period. Ensuring adequate calcium intake may be important for a variety of reasons, including its role as part of an intervention that includes another agent such as vitamin D or bisphosphonates. The magnitude of reduction in fracture risk with calcium supplementation alone remains unclear.

Conclusions

Implications for practice

Ensuring adequate calcium intake may be important for a variety of reasons, including its role as part of an intervention that includes another agent such as vitamin D or bisphosphonates. The magnitude of reduction in fracture risk with calcium supplementation alone remains unclear.

Implications for research

Future research needs to focus on standardized outcome measures and better reporting. Future investigations should take care with the selection of study patients, the dose and formulation of calcium administration, and the measures of outcome. Measuring the BMD changes for both the spine and the hip is important as these sites will likely be most predictive of fractures. Long term studies to determine fracture data are suggested.

Internal sources of support to the review

* Clinical Epidemiology Unit, Ottawa Civic Hospital CANADA
* Department of Medicine, University of Ottawa CANADA
* Institute of Population Health, University of Ottawa CANADA

External sources of support to the review

*

Potential conflict of interest

For a detailed description of the Cochrane Musculoskeletal Review Group's (CMSG) statement on potential conflict of interest please refer to the scope document. The scope can be found on the Cochrane Library at www.cochrane.org . You must log on to the Cochrane Library and under "About the Cochrane Collaboration" select "Collaborative Review Groups - CRGs". The scope will appear when you select "Cochrane Musculoskeletal Group".

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Contribution of Reviewer(s)

BS is responsible for the overall content and interpretation of the review.

JP, BS, ZO and NK extracted data, quality assessment and contacted authors of studies for additional data.

GG, JDA, AC, PT, GW, VR and LG contributed expertise in methodology, clinical interpretation and biostatistics.

CD provided editorial input. The Osteoporosis Methodology Group and the Osteoporosis Research Advisory Group provided additionnal data and content expertise.

Synopsis

HOW WELL DOES CALCIUM SUPPLEMENTS WORK TO PREVENT BONE LOSS IN WOMEN AFTER MENOPAUSE?

To answer this question, scientists analysed 15 high quality studies. These studies tested over 1800 women after menopause. Women received either a placebo (sugar pill) or 500 to 2000 mg of calcium supplements daily, including calcium gluconate, calcium carbonate, calcium citrate or salt with or without vitamin D. These studies provide the best evidence we have today.

Why does bone loss occur and how can calcium supplements help?
Bone loss may occur more quickly in women after menopause due to hormonal changes and occurs when calcium leaks out the bones. Bone loss leads to bones that are not dense and can lead to osteoporosis, a condition of weak brittle bones that break easily. Calcium is found in many foods and available as a pill for people who would like to add more calcium to their diet. It is thought that taking calcium supplements may help prevent bone loss (osteoporosis) and fractures.
How well did calcium supplements prevent bone loss and decrease fractures?
A bone mineral density test that measures how dense bones are, showed that the amount of bone lost in women taking calcium supplements taken for 2 or more years was less than the amount of bone lost in

women who took a placebo.

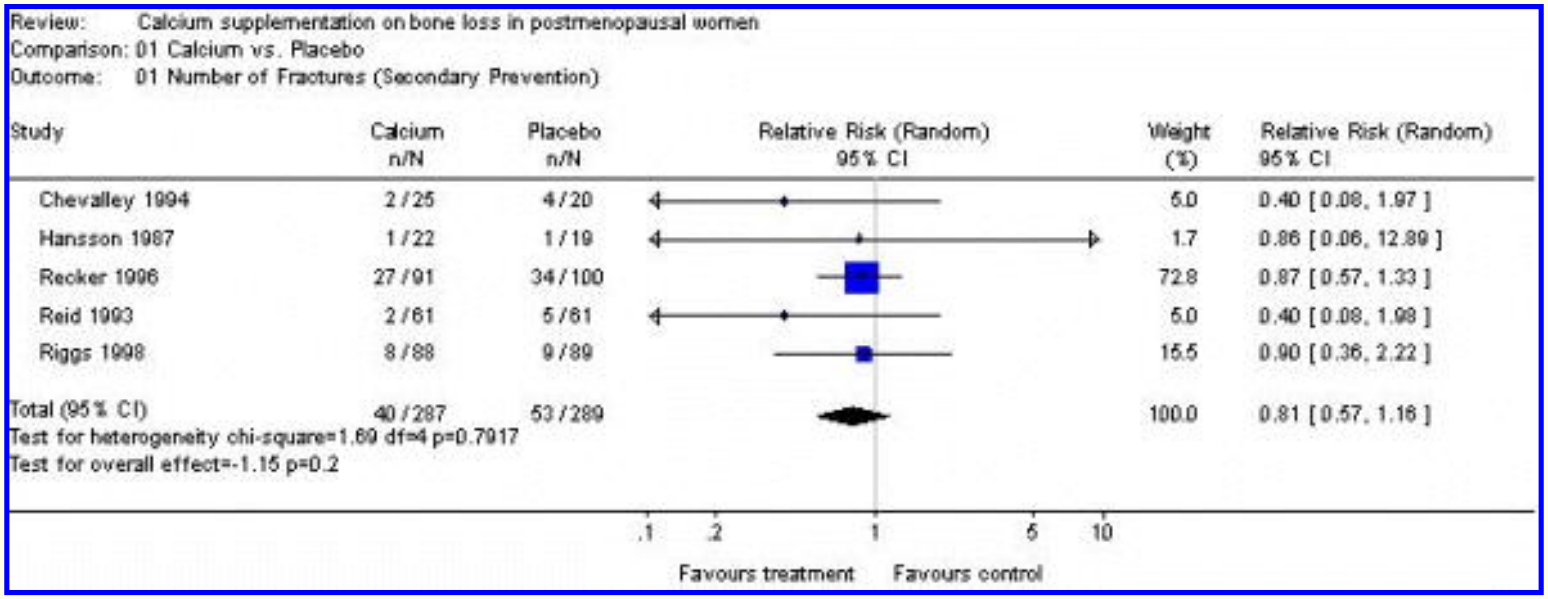
There are not many studies or large studies that measure whether calcium supplements prevent fractures. But the results from the small studies show a trend towards a decrease in spine fractures with calcium supplements and a smaller trend for non-spinal fractures, such as hip and wrist.

Were there any side effects?
Side effects were not analysed in this review. But side effects, such as stomach upset and constipation may occur.
What is the bottom line?
There is "silver" level evidence that in women after menopause, calcium supplements taken for two or more years prevents bone loss.

Calcium supplements may decrease the chances of spine fractures, but it is not known whether calcium decreases non-spinal fractures. It is important to have an adequate amount of calcium. Calcium supplements, such as calcium gluconate, calcium carbonate, calcium citrate or salt with or without vitamin D at 500 to 2000 mg daily, are the simplest and least expensive way to prevent bone loss.

Table of comparisons

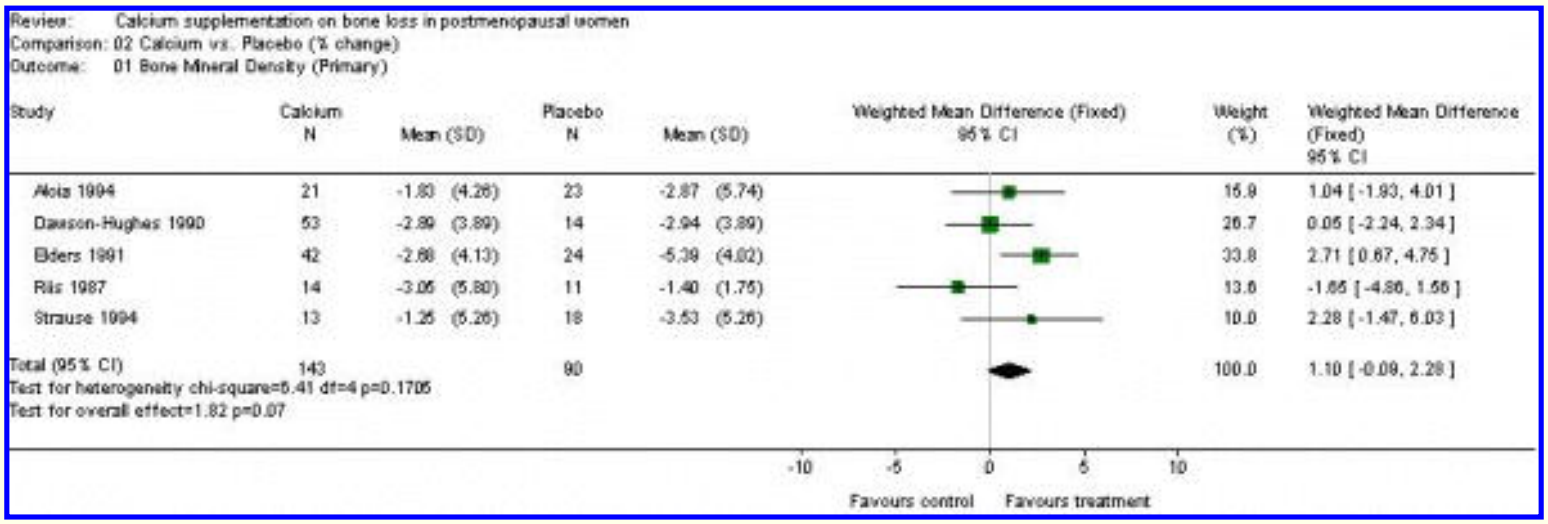
Fig 01 Calcium vs. Placebo



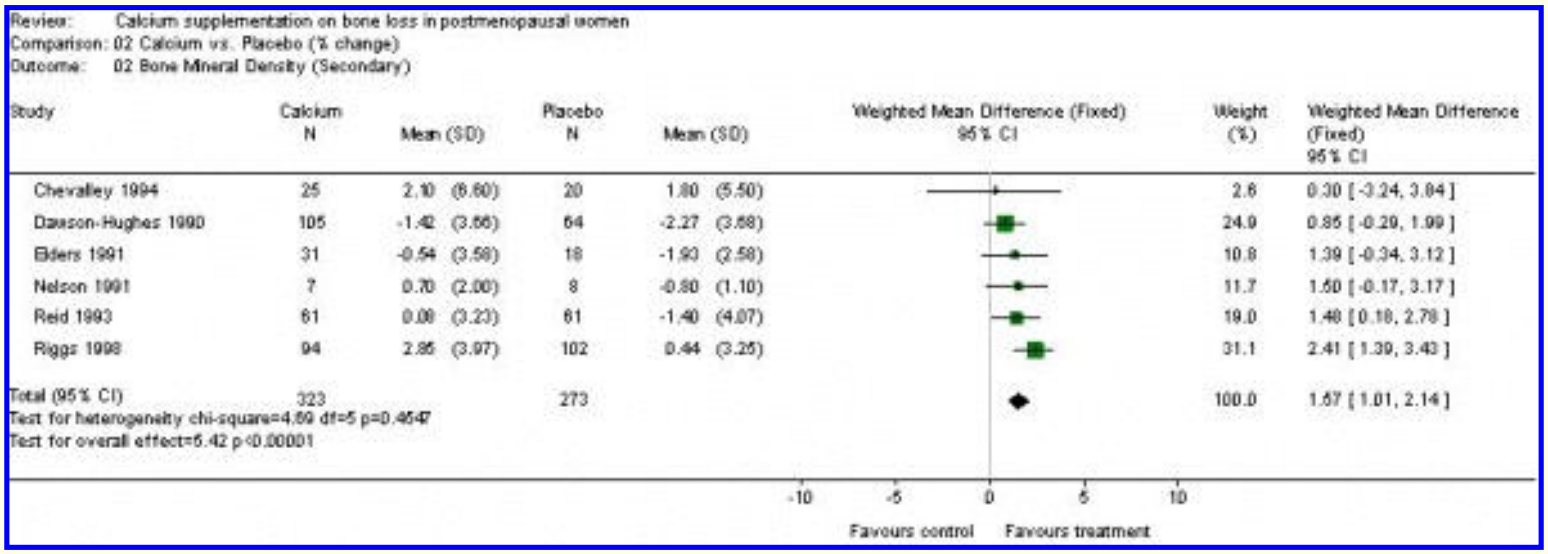
Number of Fractures (Secondary Prevention)

Table of comparisons

Fig 02 Calcium vs. Placebo (% change)



Bone Mineral Density (Primary)



Bone Mineral Density (Secondary)

Characteristics of included studies

Study: Aloia 1994

Methods: Randomized double blind placebo controlled clinical trial

Efficacy

A Parallel Study Design

Participants: Treatment/Control: 38/40

Mean Age (SD): 51.8 (1.7)

BMD: 1.01 g/cm2 (0.06)

t-score: 0.0

0% vertebral fracture prevalance

Baseline Dietary Calcium Intake (SD): 481 (114) mg/day

Interventions: Cacium Carbonate 600 mg vs placebo

(400 IU vitamin D/day)

Duration: 3 years

Outcomes: BMD: Lumbar spine, femoral neck, trochanter, total body, 1/3 radius, Wards triangle

Lost to follow up: 8/78 (10.3%)

Notes: Quality Score = 4

Allocation concealment: D

Study: Chevalley 1994

Methods: Randomized double blind placebo controlled clinical trial

Efficacy

A Parallel Study Design

Participants: Treatment/Control: 31/31

Mean Age (SD): 72.1 (0.6)

SMD: 0.98 g/cm2 (0.02)

t-score: -0.6

0% recent hip fracture prevalence

Baseline Dietary Calcium Intake (SD): 619 (318) mg/day

Interventions: Calcium carbonate 800 mg, vs placebo or Osseino mineral complex

300,000 IU vitamin D at study start

Duration: 1.5 years

Outcomes: BMD: femoral neck, femoral shaft

Fractures: vertebral and non-vertebral

Lost to follow up: 10/62 (16.1%)

Notes: Quality Score =3

Allocation concealment: D

Study: Dawson-Hughes 1990

Methods: Randomized double blind placebo controlled clinical trial

Efficacy

A Parallel Study Design

Participants: Treatment/Control: 238/123

Mean Age (SD): 58.4 (4.8)

BMD: 0.91 g/cm2 (0.02)

t-score: -1.3

0% non traumatic fracture prevalence

Baseline Dietary Calcium Intake (SD): 406 (84) mg/day

Interventions: Calcium carbonate 500mg, calcium citrate malate 500mg, versus placebo

Duration: 2 years

Outcomes: BMD: Lumbar spine, femoral neck, 1/3 radius

Lost to follow up: 46/361 (12.7 %)

Notes:

Allocation concealment: D

Study: Elders 1991

Methods: Randomized double blind placebo controlled clinical trial

Efficacy

A Parallel Study Design

Participants: Treatment/Control: 198/97

Mean Age (SD): 46-55

BMD: 0.88 g/cm2 (0.13)

t-score: -1.5

Independent of fracture prevalence

Baseline Dietary Calcium Intake (SD): 1150 (1082) mg/day

Interventions: Calcium carbonate 1000mg or 2000 mg versus placebo

Duration: 2 years

Outcomes: BMD: Lumbar spine

Lost to follow up: 47/295 (15.9%)

Notes:

Allocation concealment: D

Study: Hansson 1987

Methods: Randomized double blind placebo controlled clinical trial

Efficacy

A Parallel Study Design

Participants: Treatment/Control: 25/25

Mean Age (SD): 66.0 (6.0)

BMD: 273 mg/mm

t-score: -

100% vertebral fracture prevalence

Baseline Dietary Calcium Intake (SD): Not Available

Interventions: Calcium gluconate 1000 mg daily versus placebo

Duration: 3 years

Outcomes: BMC: Lumbar spine

Fractures: vertebral

Lost to follow up: 9/50 (18%)

Notes:

Allocation concealment: D

Study: Lamke 1978

Methods: Randomized double blind placebo controlled clinical trial

Efficacy

A Parallel Study Design

Participants: Treatment/Control: 20/20

Mean Age (SD): 60.0 (3.0)

BMD: 256 mg/mm (42)

t-score: -

100% forearm fracture prevalence

Baseline Dietary Calcium Intake (SD): Not collected

Interventions: Calcium 1000 mg versus placebo

Duration: 1 year

Outcomes: BMC: Femoral neck and femoral shaft

Lost to follow up: 4/40 (10%)

Notes: Quality Score = 2

*The authors carried out a case control study to look at BMD of patients with Colles' fractures. They later randomized the same group to receive placebo or calcium.

Allocation concealment: D

Study: Nelson 1991

Methods: Randomized double blind placebo controlled clinical trial

Efficacy

A Parallel Study Design

Participants: Treatment/Control: 19/22

Mean Age (SD): 60.2 (6.5)

BMD: 0.93 g/cm2 (0.06)

t-score: -1.1

Independent of fracture prevalence

Baseline Dietary Calcium Intake (SD): 879 (534) mg/day

Interventions: Calcium 831 mg and exercise, calcium 831 mg alone, exercise alone or placebo

Duration: 1 year

Outcomes: BMD: Lumbar spine, proximal femur and distal radius

Lost to follow up: 5/41 (12.2%)

Notes:

Allocation concealment: D

Study: Prince 1991

Methods: Randomized double blind placebo controlled clinical trial

Efficacy

A Parallel Study Design

Participants: Treatment/Control: 39/41

Mean Age (SD): 56.0 (4.0)

BMD: 272 mg/mm (31)

t-score: -

Independent of fracture prevalence

Baseline Dietary Calcium Intake (SD): 781 (300) mg/day

Interventions: Calcium gluconate 1000 mg plus exercise versus exercise alone

Duration: 2 years

Outcomes: BMD: Distal, median and proximal forearm

Lost to follow up: 10/80 (12.5%)

Notes:

Allocation concealment: D

Study: Prince 1995

Methods: Randomized double blind placebo controlled clinical trial

Efficacy

A Parallel Study Design

Participants: Treatment/Control: 42/42

Mean Age (SD): 62.5 (4.5)

BMD: 0.87 g/cm2 (0.13)

t-score: -1.6

Baseline Dietary Calcium Intake (SD): 804 (299) mg/day

Interventions: Calcium lactate gluconate 1000 mg versus placebo, also calcium and exercise and milk powder group (not included)

Duration: 2 years

Outcomes: BMD: Total spine, femoral neck, total hip, interotrochanteric, trochanter, ultradistal ankle

Lost to follow up: 13/84 (15.5%)

Notes: Quality score = 2

Allocation concealment: D

Study: Recker 1996

Methods: Randomized double blind placebo controlled clinical trial

Efficacy

A Parallel Study Design

Participants: Treatment/Control: 93/104 Fractures 52/42

No Fractures 41/62

Mean Age (SD): 73.5 (7.1)

BMD: 0.727g (0.14)

t-score: -

47.7% vertebral fracture prevalence

Baseline Dietary Calcium Intake (SD): 431 (194) mg/day

Interventions: Calcium carbonate 1200 mg versus placebo

Duration: 4 years

Outcomes: BMC: Distal forearm

Fractures: vertebral fractures

Lost to follow up: 17/197 (8.6%)

Notes:

Allocation concealment: D

Study: Reid 1993

Methods: Randomized double blind placebo controlled clinical trial

Efficacy

A Parallel Study Design

Participants: Treatment/Control: 68/67

Mean Age (SD): 58.0 (5.0)

BMD: 0.87 g/cm2 (0.14)

t-score: -1.6

0% symptomatic vertebral fractures prevalence

Baseline Dietary Calcium Intake (SD): 745 (298) mg/day

Interventions: Calcium 1000 mgs versus placebo

Duration: 2 years

Outcomes: BMD: Lumbar spine, proximal femur, total body

Fractures: symptomatic vertebral fractures

Lost to follow up: 13/135 (9.6%)

Notes: Quality Score= 4

Allocation concealment: D

Study: Riggs 1998

Methods: Randomized double blind placebo controlled clinical trial

Efficacy

A Parallel Study Design

Participants: Treatment/Control: 119/117

Mean Age (SD): 66.3 (2.6)

BMD: 0.91 g/cm2 (0.10)

t-score: -1.2

0% vertebral fracture prevalence

Baseline Dietary Calcium Intake (SD): 714 (286) mg/day

Interventions: Calcium citrate salt 1600 mg versus placebo

Duration: 4 years

Outcomes: BMD: Lumbar spine, total body, total hip

Fractures: vertebral and non vertebral

Lost to follow up: 59/236 (25%)

Notes:

Allocation concealment: D

Study: Riis 1987

Methods: Randomized double blind placebo controlled clinical trial

Efficacy

A Parallel Study Design

Participants: Treatment/Control: 15/13

Mean Age (SD): 50 (2.8)

BMD: 0.72 g/cm2 (0.15)

t-score: -3.0

Independent of fracture prevalence

Baseline Dietary Calcium Intake (SD): Not collected (800mg national average)

Interventions: Calcium carbonate 2000 mg versus placebo

Duration: 2 years

Outcomes: BMD: Lumbar spine, total body, distal forearm, proximal forearm

Lost to follow up: 3/28 (10.7%)

Notes: Quality Score = 4

The code was broken after the first year to add progesterone to the estrogen group. The calcium group remained blinded

Discription of randomization slightly confusing

Allocation concealment: D

Study: Smith 1989

Methods: Randomized double blind placebo controlled clinical trial

Efficacy

A Parallel Study Design

Participants: Treatment/Control: 44/38

Mean Age (SD): 55 (4.7)

BMD: 0.68 g/cm2

t-score: -

Independent of fracture prevalence

Baseline Dietary Calcium Intake (SD): 679 (237) mg/day

Interventions: Calcium 500 mg versus placebo

Duration: 4 years

Outcomes: BMC and BMD: Radius, ulna, and humerus

Lost to follow up: 15/82 (18.3%)

Notes: Quality Score = 4

Allocation concealment: D

Study: Strause 1994

Methods: Randomized double blind placebo controlled clinical trial

Efficacy

A Parallel Study Design

Participants: Treatment/Control: 29/28

Mean Age (SD): 65.4 (5.3)

BMD: 0.92 g/cm2 (0.15)

t-score: -1.2

Independent of fracture prevalence

Baseline Dietary Calcium Intake (SD): 572 (288) mg/day

Interventions: Calcium citrate malate 1000mg versus placebo or trace minerals with/out calcium

Duration: 2 years

Outcomes: BMD: Lumbar Spine

Lost to follow up: 31/57 (57.4%)

Notes: Quality Score = 2

Allocation concealment: D

BMD = Bone Mineral Density BMC = Bone Mineral ContentDPA = Dual Photon AbsorptiometryDXA = Dual X-Ray AbsorptiometrySPA = Single-Photon Absorptiometry

Characteristics of excluded studies

Study: Chapuy 1992

Reason for exclusion: They used as intervention Vit D in doses higher than 400 UI per day

Study: Dawson-Hughes 1997

Reason for exclusion: In combination with Vit D

Study: Lau 1992

Reason for exclusion: Only 10 months duration

Study: Orwell 1990

Reason for exclusion: Only included male subjects.

Study: Polley 1987

Reason for exclusion: Did not meet inclusion criteria. The outcome (BMD Forearm) was not measured using one of the following SPA, DPA or DXA. The densitometry was performed using a molsgaard bone mineral analyzer 1100.

Study: Recker 1977

Reason for exclusion: A priori selected outcomes not included.

Study: Recker 1985

Reason for exclusion: A priori selected outcomes not included.

Study: Smith 1981

Reason for exclusion: Type of intervention- no calcium only group.

Table 02 Weighted Relative Risk of Fracture After Treatment with Calcium

Fracture Site: Vertebral

Number of Trials: 5

Sample Size: 576

Relative Risk (95% C: 0.79 (0.55, 1.13)

Relative Risk p-valu: 0.14

Hetergeneity p-value: 0.40

Fracture Site: Non Vertebral

Number of Trials: 2

Sample Size: 222

Relative Risk (95% C: 0.86 (0.43, 1.72)

Relative Risk p-valu: 0.66

Hetergeneity p-value: 0.54

Table 03 Weighted Mean Difference of Bone Density after Treatment with Calcium

Bone Density Site: Total Body

Number of Trials: 4

Sample Size (N): 358

Weighted Mean Differ: 2.05 (0.24, 3.86)

p-value: 0.03

Test of Heterogeneit: <0.01

Bone Density Site: Lumbar Spine (2 year)

Number of Trials: 9

Sample Size (N): 845

Weighted Mean Differ: 1.66 (0.92, 2.39)

p-value: <0.01

Test of Heterogeneit: 0.02

Bone Density Site: Lumbar Spine (3 or 4 year)

Number of Trials: 2

Sample Size (N): 218

Weighted Mean Differ: 1.13 (-0.11, 2.38)

p-value: 0.07

Test of Heterogeneit: 0.71

Bone Density Site: Combined Hip

Number of Trials: 8

Sample Size (N): 830

Weighted Mean Differ: 1.64 (0.70, 2.57)

p-value: <0.01

Test of Heterogeneit: 0.04

Bone Density Site: 1/3 Distal Radius

Number of Trials: 6

Sample Size (N): 615

Weighted Mean Differ: 1.91 (0.33, 3.50)

p-value: 0.02

Test of Heterogeneit: <0.01

Table 04 Heterogeneity of Difference of Bone Mineral Density

Bone Density Site: Total Body

Heterogeneity p-valu: <0.01

Primary; Secondary: 4.50; 0.59

3.91 (1.18, 6.64)

p=0.01

Loss to Follow-up: 2.91; 0.37

2.54 (-1.06, 6.14)

p=0.17

Calcium Supplementat: 0.63; 5.50

-4.87 (-6.80, -2.93)

p <0.01

Baseline Daily Calci: 0.82; 2.86

-2.05 (-7.12, 3.02)

p=0.43

Site Measured Total: One Site Only

Bone Density Site: Lumbar Spine (2 years)

Heterogeneity p-valu: 0.02

Primary; Secondary: 1.06; 1.86

-0.80 (-2.51, 0.92)

p=0.36

Loss to Follow-up: 1.32, 2.17

-0.35 (-2.24, 0.53)

p=0.23

Calcium Supplementat: 2.00; 0.74

1.27 (0.02, 2.51)

p=0.05

Baseline Daily Calci: 1.87; 1.39

0.48 (-0.94, 1.90)

p=0.51

Site Measured Total: One Site Only

Bone Density Site: Lumbar Spine (3-4 years)

Heterogeneity p-valu: 0.71

Primary; Secondary: 0.65; 1.25

-0.60 (-3.76, 2.57)

p=0.71

Loss to Follow-up: 0.65; 1.25

-0.60 (-3.76, 2.57)

p=0.71

Calcium Supplementat: 1.25; 0.65

0.60 (-2.57, 3.76)

p=0.71

Baseline Daily Calci: Only 1 subgroup

Site Measured Total: One Site Only

Bone Density Site: Combined Hip

Heterogeneity p-valu: 0.04

Primary; Secondary: 2.78; 1.51

1.27 (-4.04, 6.57)

p=0.64

Loss to Follow-up: 1.78; 1.45

0.33 (-1.43, 2.10)

p=0.71

Calcium Supplementat: 1.53; 2.11

0.57 (-3.28, 2.14)

p=0.68

Baseline Daily Calci: 1.55; 1.70

-0.14 (-2.15, 1.86)

p=0.89

Site Measured Total: 1.37; 1.87

-0.50 (-2.16, 1.16)

p=0.55

Bone Density Site: 1/3 Distal Radius

Heterogeneity p-valu: <0.01

Primary; Secondary: 2.51; 1.71

0.81 (-1.80, 3.41)

p=0.54

Loss to Follow-up: 1.70; 3.44

-1.74 (-4.55, 1.06)

p=0.22

Calcium Supplementat: 2.30; 1.18

1.12 (-1.54, 3.78)

p=0.41

Baseline Daily Calci: 1.05; 2.35

-1.30 (-4.70, 2.10)

p=0.45

Site Measured Total: One Site Only

Table 05 Difference of Bone Mineral Density by Calcium Type

Bone Density Site: Total Body

Heterogeneity p-valu: <0.01

Calcium Citrate;: 0.37; 4.50

-4.13 (-6.93, -1.33)

p<0.01

Calcium Citrate; Cal:

Calcium Carbonate;:

Bone Density Site: Lumbar Spine (2 years)

Heterogeneity p-valu: 0.34

Calcium Citrate;: 2.41; 1.24

1.17 (-0.43, 2.77)

p=0.15

Calcium Citrate; Cal:

Calcium Carbonate;:

Bone Density Site: Lumbar Spine (3-4 years)

Heterogeneity p-valu: 0.71

Calcium Citrate;: 1.25; 0.65

0.60 (-2.57, 3.76)

p=0.71

Calcium Citrate; Cal:

Calcium Carbonate;:

Bone Density Site: Combined Hip

Heterogeneity p-valu: 0.15

Calcium Citrate;: 1.15; 4.19

-3.03 (-5.92, -0.15)

p=0.04

Calcium Citrate; Cal: 1.15; 1.61

-0.46 (-2.17, 1.26)

p=0.60

Calcium Carbonate;: 4.19; 1.61

2.58 (-0.33, 5.48)

p=0.08

Bone Density Site: 1/3 Distal Radius

Heterogeneity p-valu: 0.16

Calcium Citrate;:-; 2.83

(only 1 subgroup)

Calcium Citrate; Cal:

Calcium Carbonate;:

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