Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D_3) for prevention of fractures in primary care

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Abstract

Objective To assess whether supplementation with calcium and cholecaliferol (vitamin D_3) reduces the risk of fracture in women with one or more risk factors for fracture of the hip.
Design Pragmatic open randomised controlled trial.
Setting Practice nurse led clinics in primary care.
Participants 3314 women aged 70 and over with one or more risk factors for hip fracture: any previous fracture, low body weight (< 58 kg), smoker, family history of hip fracture, or fair or poor self reported health.
Intervention Daily oral supplementation using 1000 mg calcium with 800 IU cholecaliferol and information leaflet on dietary calcium intake and prevention of falls, or leaflet only (control group).
Main outcome measures Primary outcome measure was all clinical fractures and secondary outcome measures were adherence to treatment, falls, and quality of life (measured with the SF-12).
Results 69% of the women who completed the follow-up questionnaire at 24 months were still taking supplements (55% with inclusion of randomised participants known to be alive). After a median follow-up of 25 months (range 18 to 42 months), clinical fracture rates were lower than expected in both groups but did not significantly differ for all clinical fractures (odds ratio for fracture in supplemented group 1.01, 95% confidence interval 0.71 to 1.43). The odds ratio for hip fracture was 0.75 (0.31 to 1.78). The odds of a woman having a fall at six and 12 months was 0.99 and 0.98, respectively. Quality of life did not significantly differ between the groups.
Conclusion We found no evidence that calcium and vitamin D supplementation reduces the risk of clinical fractures in women with one or more risk factors for hip fracture.
Registration ISRCTN26118436, controlled trials registry.

Introduction

Low trauma fractures represent a major burden of illness and cost to society.[1–3] This burden is likely to increase with ageing populations and because the age specific incidence of hip fracture seems to be increasing.[4] Effective strategies are needed in a community setting to prevent the continuing rise in hip and other fractures and to reduce the associated excess morbidity and cost.

One relatively inexpensive method of reducing fracture rates might be supplementation with calcium and vitamin D. A randomised trial among female residents of French nursing homes showed significant reductions in both hip and non-hip fractures among those assigned supplementation with calcium and cholecaliferol (vitamin D_3),[5] and a study among community dwelling American men and women also noted a reduction in non-vertebral fractures in women receiving supplementation.[6] More recently another study among women in French nursing homes noted a large but statistically non-significant reduction in hip, but not non-hip, fractures among those assigned calcium and vitamin D supplementation.[7] The only trial that had fracture as the main end point was the original French nursing home study. It remains unknown whether these results can be generalised to populations outside of institutional care settings in France. Supplementation with calcium and vitamin D might be expected to prevent fractures not only through reductions in bone loss but by reducing falls. A recent systematic review found that vitamin D supplementation can reduce falls and falling by 22%.[8]

We assessed whether giving calcium and vitamin D supplements to community dwelling older women at increased risk of hip fracture would reduce their risk of any fracture.

Participants and methods

We identified women aged 70 and over who had at least one self reported risk factor for hip fracture: low bodyweight (< 58 kg), any previous fracture, maternal history of hip fracture, smoker, and poor or fair health. These risk factors were taken from a large population study in the United States[9]: we subsequently confirmed in a British cohort study that, apart from smoking, these risk factors predict the risk of hip and non-hip fractures.[10] We assessed self reported calcium consumption through a brief 10 item questionnaire that was sent to the women along with questions on risk factors for fracture.

Women were excluded from the study if they could not give written consent or were receiving any calcium supplementation of more than 500 mg a day. We also excluded women with a history of kidney or bladder stones, renal failure, or hypercalcaemia.

Details of previous trials are on bmj.com

Scientic information - clinical documentation

The clinical documentation is based on published scientific data with calcium-citrate-malate and vitamin D.

1. Absorption of calcium-citrate-malate

Animal and human studies have demonstrated an excellent absorption of calcium from calcium-citrate-malate (1). Comparative studies with calcium-citrate-malate and calcium carbonate showed a significant higher absorption of calcium-citrate-malate (2). In the cited studies calcium absorption was evaluated by the use of radioactive isotopes (1, 2). This methods is regarded the most valid method for investigating calcium absorption. Clear differences are observed when analysing studies where calcium absorption was measured by the use of radioactive isotopes. Besides a difference in mean calcium absorption of 36.2 % from calcium-citrate-malate compared to 26.4 % from calcium carbonate the range of calcium absorption differed as well between the two preparations (1-3). Absorption from calcium-citrate-malate ranged from 27-53 % and 12-39 % from calcium carbonate (1-3). In contrast to calcium carbonate the absorption of calcium-citrate-malate proved independent of the presence of gastric acid or co-ingested food (4). However, gastric acid is important in order to absorb calcium carbonate between meals (5). This finding has major clinical importance since gastric acid secretion is completely absent in 10 % of females above 50 years and approximately 40 % of females do not secret gastric acid between meals (6). In addition calcium absorption may be extremely low in young healthy subjects with normal gastric acid output unless this substance is taken with a meal (4). There is no easy way to ensure whether a person, young or elderly, is capable of absorbing calcium from calcium carbonate. So far no non-calcium absorbers have been encountered with the use of calcium-citrate-malate.

Studies have demonstrated that except for calcium-citrate-malate (7), ingestion of calcium at mealtime may induce iron deficiency (8). Even a daily intake of 1000 mg calcium-citrate-malate has recently been shown not to influence significantly on iron absorption (9).

2. Calcium-citrate-malate and bone mineral density

The superior characteristics of calcium-citrate-malate compared to calcium carbonate and milk (1, 2) are also present when investigating the effect of calcium supplementation on bone mineral density. A two-year double-blind placebo-controlled trial conducted in post menopausal females revealed that calcium-citrate-malate was more effective in reducing bone loss compared to calcium carbonate (10). In addition, in females with an average calcium intake below 400 mg/day supplementation with 500 mg calcium-citrate-malate increased bone mineral density significantly (10).

Placebo-controlled trials including larger groups of adolescent twins have demonstrated clear and significant increases in bone mineral density in children and adolescent with this calcium compound (11, 12).

3. Vitamin D_3

Vitamin D_3 is a fat-soluble vitamin that is readily absorbed from the intestine. In the liver Vitamin D_3 is converted to 25-vitamin D_3 through hydroxylation. Subsequently 25-vitamin D_3 undergoes hydroxylation to 1,25-dihydroxy-vitamin D_3. 1,25-dihydroxy-vitamin D_3 is the physiologically active form of vitamin D. The absorption of calcium from the intestine is an active 1,25-dihydroxy-vitamin D3 dependent pro-

cess (13, 14). Kinetic studies have demonstrated a limited capacity of the 1,25-dihydroxy-vitamin D_3 dependent pathway (15). This finding explains why calcium loads above 5-600 mg only results in a limited additional rise in the amount of absorbed calcium (15). From the age of 40 to 60 years a decline in calcium absorption of 20 to 25 % is observed (16). This is partly caused by a reduced amount of vitamin D receptors in the small intestine and a reduced hydroxylation capacity of the kidney with age (17, 18). Vitamin D-deficiency is common in the elderly in western countries and vitamin D therapy has shown to reduce osteoporotic fractures in elderly people (19-22). Recent studies have demonstrated that a daily intake of 400-800 IU vitamin D3 is beneficial and also safe (20, 23, 24).

4. Calcium and vitamin D in the treatment of osteoporosis

Calcium-citrate-malate alone has been shown to increase bone mineral density in younger individuals and prevent or slow calcium loss in postmenopausal females (10, 11, 25). A recent 3 year double-blind placebo-controlled trial conducted in males and females beyond 65 years of age used 500 mg calcium-citrate-malate and 600 to 800 IU vitamin D3 (26). The study demonstrated a significant gain in total body calcium and a significant reduction in the number of non-vertebral fractures (26). A French study demonstrated a reduction in the number of non-vertebral fractures in elderly females with the use of 800 IU of vitamin D3 and 1200 mg calcium as tri-calcium-phosphate (20). A reduction in fracture incidence has only been reported in patients already experiencing a previous fracture with the use of 1200 mg calcium as calcium carbonate (27). However, calcium carbonate did not have any effect of fracture incidence in subjects without a previous fracture (27).

5. Tolerability and safety of calcium-citrate-malate and vitamin D_3

In the above-cited studies with calcium-citrate-malate (duration up to 3 years) the side effects were comparable to placebo. In addition no serious side effects have been observed in long-term treatment with 1000 mg/day (12).

6. Effectiveness and optimal dosing of calcium and vitamin D

The effectiveness of calcium and vitamin D in the prevention and treatment of osteoporosis has been questioned in part due to inconsistent study results with other calcium sources (28-31). All studies with the use of calcium-citrate-malate as the calcium source, either given alone or in combination with vitamin D, have demonstrated clear effects in pre-pubertal girls, adolescents and postmenopausal women (10-12, 25, 26, 32).

Based on the above cited scientific evidence including the most recent randomised double-blinded placebo-controlled study an intake of 600 mg calcium-citrate-malate and 600 IU of vitamin D3 seems justified, safe and well documented (26).

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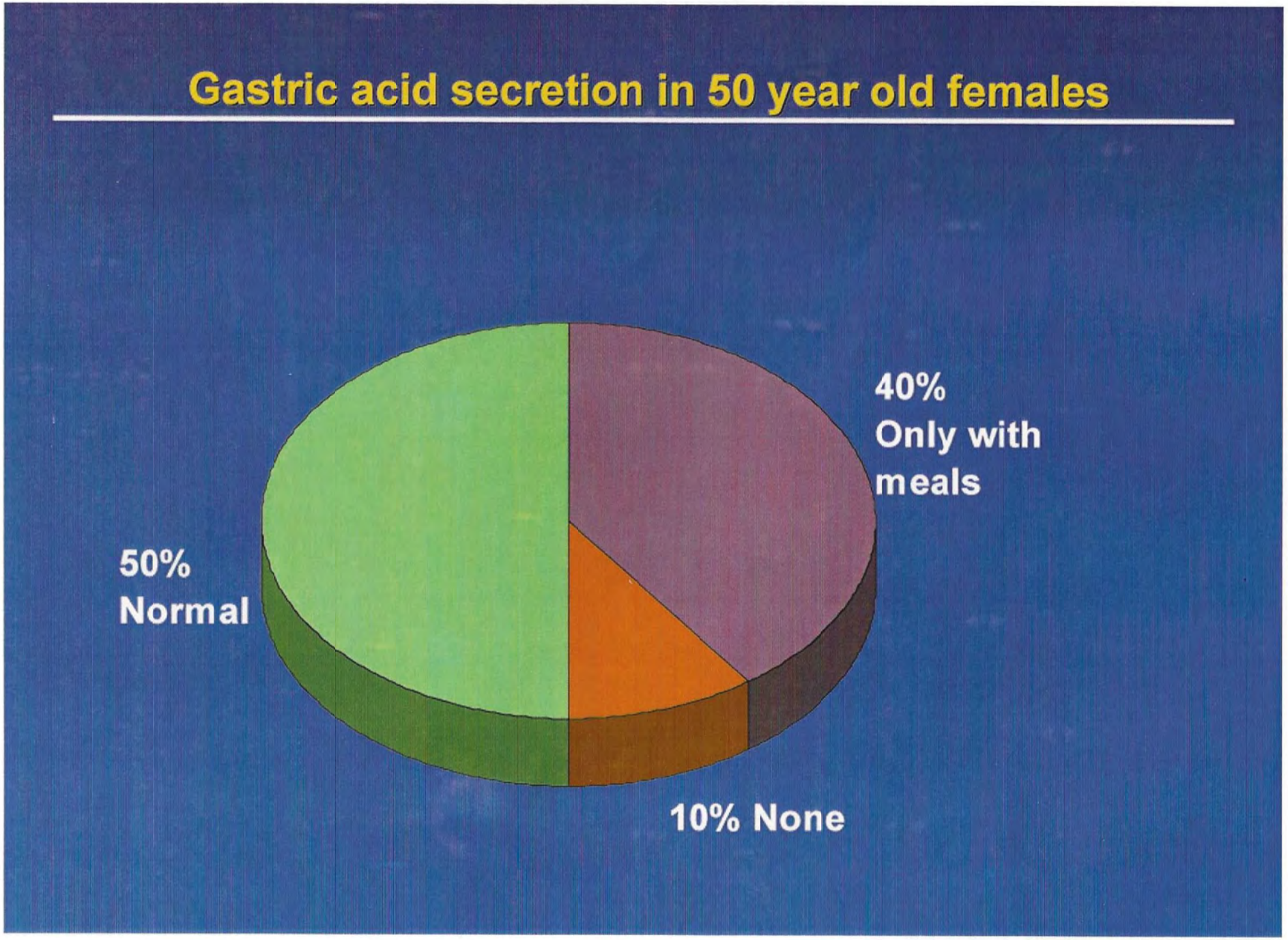
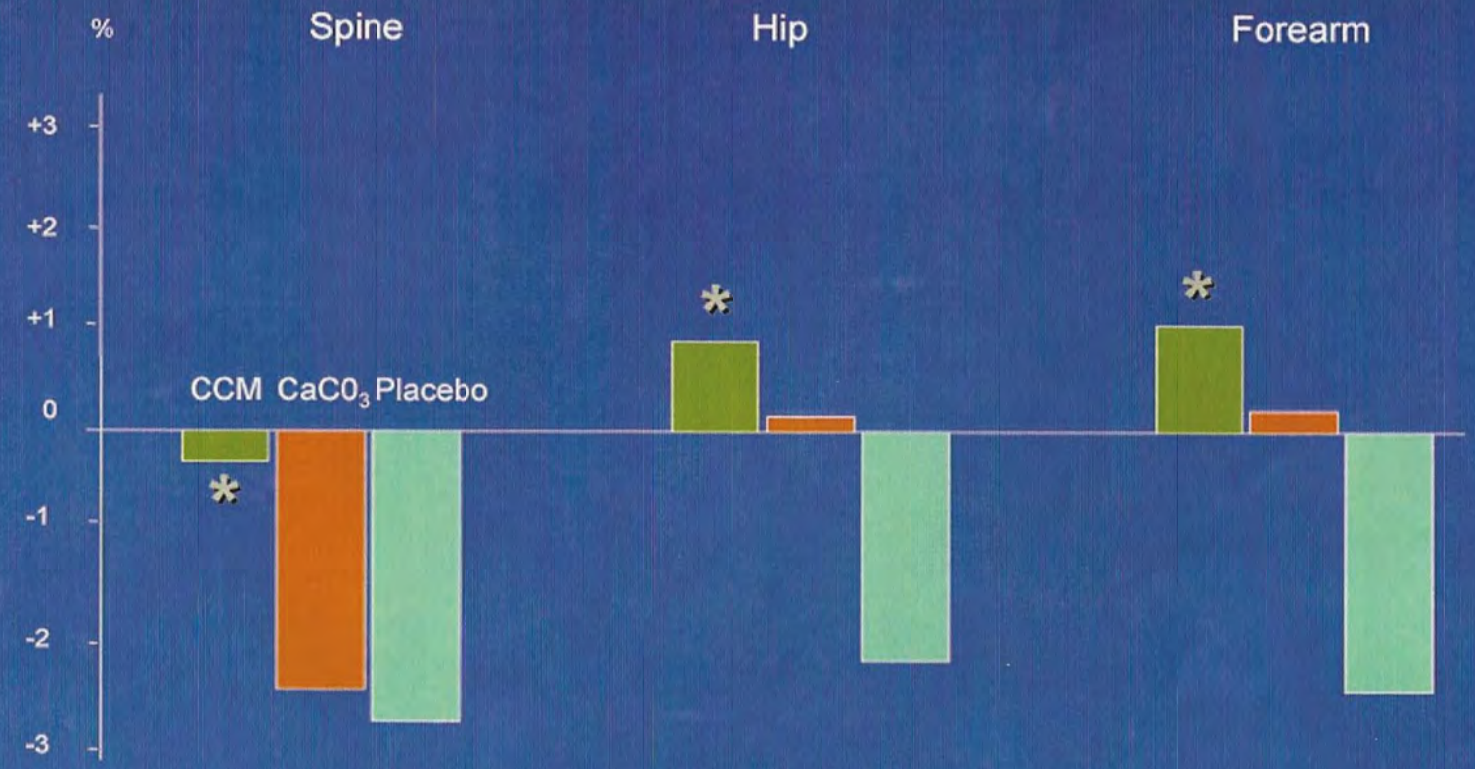

Gastric acid secretion in 50 year old females
40%
Only with
meals
50%
Normal
10% None

Differences in bioavailability of calcium compunds measured on BMD

2 years placebo-controlled treatment with 500 mg elemental calcium given as calcium-citrate-malate (CCM) or Calciumcarbonat ($CaCO_3$)



Calcium-citrate-malate (CCM) is 4-6 times more potent than Calciumcarbonat ($CaCO_3$)

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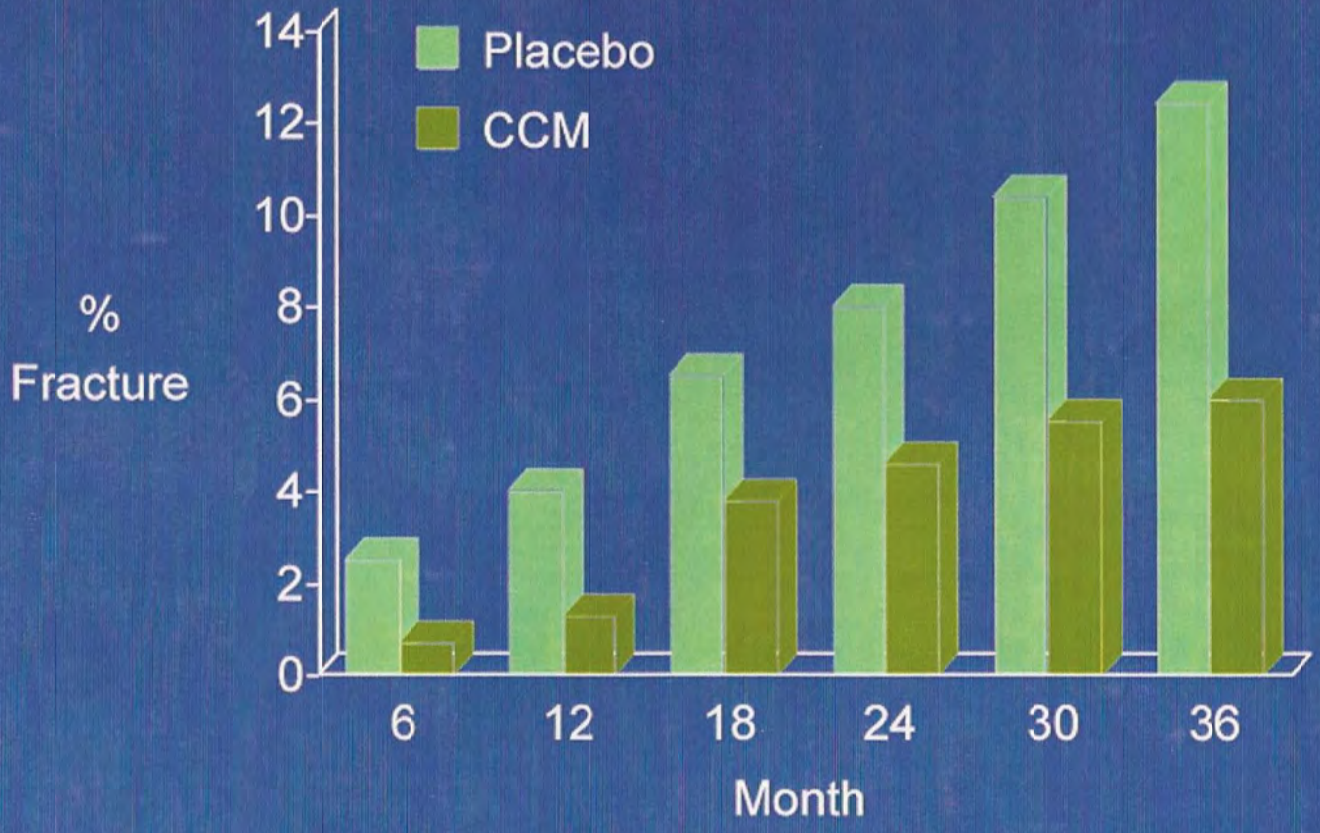
Calcium-Citrate-Malate (CCM) prevents fractures



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