

Evidence that Calcium Supplements Reduce Fracture Risk Is Lacking

Ego Seeman

Austin Health, University of Melbourne, Melbourne, Australia

Credible evidence that calcium supplements reduce the risk of vertebral, nonvertebral, or hip fractures is lacking. Flaws in study design and execution such as inclusion of calcium-replete individuals, high dropout rates, and poor compliance preclude testing the hypothesis that calcium deficiency increases fracture rates or that calcium supplements reduce them. Intent-to-treat analyses of individual trials have failed to detect antifracture efficacy. *Post hoc* analyses of subgroups with a low calcium intake and per-protocol analyses of compliers have reported fewer fractures in the supplemented groups. However, this may be the result of confounding by violation of randomization; compliers to placebo have a lower morbidity and mortality than noncompliers. Higher hip fracture rates and cardiac mortality in patients receiving calcium supplements, as reported in some studies, may also be due to factors other than supplementation. Hypothesis testing requires that a cohort be stratified into calcium-deficient and calcium-replete groups, with each person randomized to a supplement or placebo. This design quantifies the risk of fracture attributable to calcium deficiency and any benefit that supplementation confers in the calcium-deficient and calcium-replete groups. To regard a calcium-deficient arm as unethical begs the question. Consensus statements that support the widespread use of calcium are opinion-based; they accept claims of beneficial effects despite flaws in study design, execution, and analysis; and they reject reported adverse effects because of them. Until well designed, well executed, and well analyzed studies demonstrate a net benefit in morbidity, mortality, and cost, recommendations supporting the widespread use of calcium supplementation remain belief-based and not evidence-based.

Clin J Am Soc Nephrol 5: S3–S11, 2010. doi: 10.2215/CJN.06160809

The burden of bone fractures in the community comes from the larger segment of the population without osteoporosis as well as the elderly (1,2). Drug therapy cannot be given to all persons because antifracture efficacy and safety remain unconfirmed in these groups and treatment costs are prohibitive (3). Therefore, alternative approaches such as lifestyle changes are needed to lower fracture risk in the population as a whole (4). Although these interventions must be efficacious, they must also have a very high level of safety because public health measures exposing many individuals at low fracture risk to rare adverse events may produce no net health benefit, as demonstrated by the study results of estrogen-progestin in the Women's Health Initiative (5). In addition, interventions must be practical (e.g., readily accessible to all, easily administered, have a high rate of compliance, and be inexpensive). Calcium supplementation may meet these requirements.

The hypothesis that calcium deficiency causes bone fragility is plausible (6–9). Because 99% of calcium resides in bone, obligatory losses from the gut, kidney, and skin of 150 to 200 mg/d must be compensated for by increased fractional calcium absorption. If fractional calcium absorption is 25%, an intake of at least 800 mg/d is required to offset these losses. Below this level, bone must be resorbed to maintain serum calcium (9). On the basis of this rationale, a “deficiency” state is

said to exist with intakes of less than approximately 800 mg daily. The requirement will be higher if fractional calcium absorption is lower and obligatory losses are greater, but it may be less if fractional calcium intake can be adaptively increased to 70 to 90% during low calcium intakes. In this case, calcium deficiency would not exist with intakes of more than 150 to 200 mg daily.

Acute Calcium Deficiency: Perturbing Steady-State Remodeling—A Few More Holes in the Bucket, without Filling It Faster

Short-term studies of calcium deprivation in humans confirm that with acute calcium deprivation, a fall in serum calcium stimulates secretion of parathyroid hormone (PTH) and increases the rate of bone remodeling (6–10). For example, elderly women taking over 2000 mg calcium daily had mean levels of 24-h serum PTH and resorption markers similar to young adult women taking 900 mg/d and below that of elderly women receiving 800 mg/d (10).

When calcium intake is low, the remodeling rate increases. The number of bone metabolic units (BMUs) appearing on the endosteal envelope increases, and resorption by each BMU removes a volume of bone along with its associated mineral content, producing a rapid 1 to 3% fall in bone mineral density (BMD) (6–9). This rapid decrease is produced by the normal delay in initiation of the formation phase of the remodeling cycle (the reversal phase). It also arises from the slower rate of osteoid deposition, with its subsequent rapid primary and slower secondary mineralization. Consequently, the increased

Correspondence: Dr. Ego Seeman, FRACP, Department of Endocrinology, Centaur Building, Repatriation Campus, Austin Health, Heidelberg 3081, Melbourne, Australia. Phone: 61-3-94965489; Fax: 61-3-9496-3365; E-mail: egos@unimelb.edu.au

number of resorption cavities appearing on the endosteal surface do not fill immediately (or more correctly, partially refill because of the negative BMU balance present in adulthood) (11).

Evidence of bone loss after an acute decrease in calcium intake is based on studies in which supplementation was stopped. Dawson-Hughes *et al.* reported that the benefits of calcium plus vitamin D on BMD achieved during 3 yr of supplementation were lost during 2 yr of follow-up (Figure 1A) (12). Prestwood *et al.* found that cessation of calcium supplementation was accompanied by an increase in remodeling and accelerated bone loss (13). This reflects perturbation of steady-state remodeling with enlargement of the transient remodeling deficit produced by increased resorptive removal of bone, without instantaneous increase in bone formation in each of the more numerous remodeling sites (Figure 1B).

Long-Term Calcium Deficiency: Steady State at a Higher Remodeling Rate

With persistent low intake of calcium, steady state is restored but at a higher remodeling rate than before the occurrence of calcium deficiency. Bone loss continues from the acute BMD reduction of 1 to 3%, but at a slower rate because bone formation has commenced in the larger numbers of excavated sites generated during acute deficiency, thus reversing the transient remodeling deficit.

Determining whether the rate of bone loss during chronic calcium deficiency is greater than that occurring before the onset of deficiency is challenging for several reasons. Bone loss

at steady state will be more rapid than before calcium deficiency by an amount determined by the increase in the remodeling rate produced by the increment in secondary hyperparathyroidism (sHPT), as well as any worsening of the negative BMU balance resulting from an increased lifespan of osteoclasts and decreased lifespan of osteoblasts (14).

However, a dose-response relationship between increasing levels of calcium deficiency, increased remodeling rate, and degree of sHPT remains unclear, and there is no evidence of increased resorption or reduced bone formation by the BMU. If BMU balance becomes more negative, the resulting increased rate of bone loss is likely to be small relative to that caused by the increased remodeling rate.

Few studies have compared the rate of bone loss during steady state in a calcium-deficient group to calcium-replete controls, perhaps because such a study is regarded as unethical, a view that begs the question. Dawson-Hughes *et al.* studied the effects of supplementation in women who were stratified by calcium intake (15). Bone loss was observed in placebo-treated subjects with calcium intake <400 mg/d, but not above this level. Bone loss was found at the radius and proximal femur but not at the spine.

Calcium Deficiency and Bone Morphology

No data exist defining structural damage produced by calcium deficiency, such as effects on increasing endocortical, intracortical, and trabecular resorption and, therefore, cortical thinning, intracortical porosity, trabecular thinning, and loss of connectivity.

If dietary calcium deficiency worsens BMU imbalance by

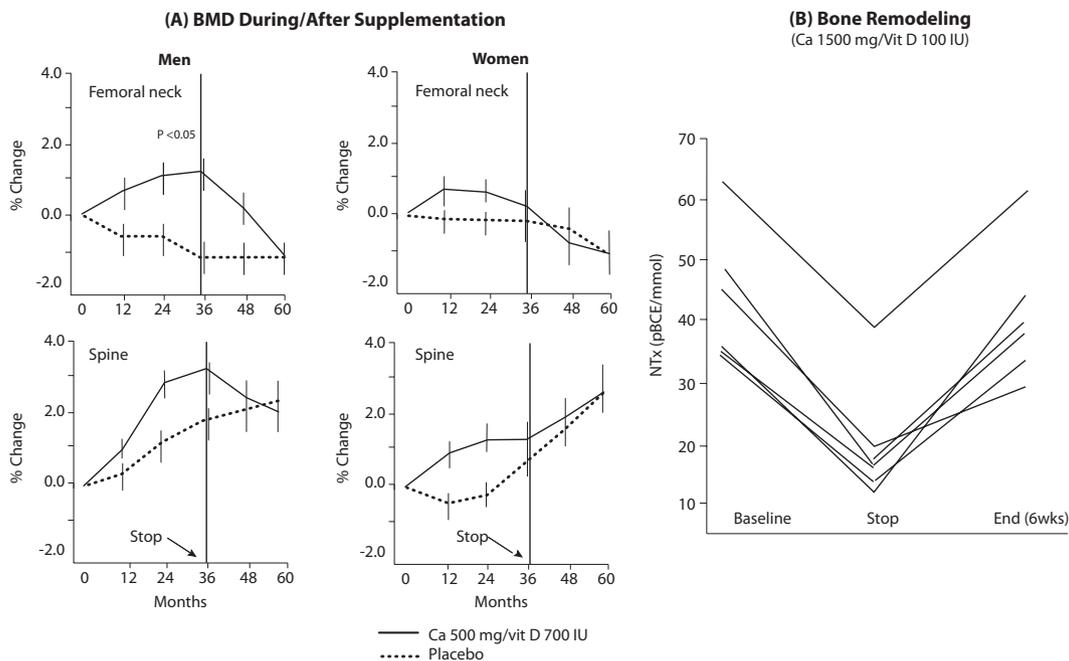


Figure 1. (A) BMD increased in women and men (aged >65 yr) at the femoral neck and spine over 3 yr then decreased when supplementation was stopped. Adapted from Dawson-Hughes *et al.* (12). (B) Calcium supplementation slowed remodeling [reflected in the decline in N-terminal telopeptide (NTx), a marker of bone resorption], then increased when supplementation was stopped. Adapted from Prestwood *et al.* (13).

increasing resorption depth due to prolonged osteoclast life-span induced by sHPT, deeper resorption cavities may produce structural decay, stress risers, and bone fragility disproportionate to the small increase in bone loss. The resulting structural damage and fragility also depend on the underlying bone structure; thicker trabeculae can tolerate more resorption, whereas thicker cortices with less porosity can withstand more intracortical and endocortical resorption. Consequently, the degree of structural damage and fragility produced by bone loss cannot be inferred from the amount of bone loss alone.

Acute Calcium Supplementation: Perturbing Steady-State Remodeling—Plugging Only a Few Holes in the Bucket while Leaving the Tap Running

When a calcium supplement is given, remodeling is suppressed by 10 to 30%. This rate is approximately half of that observed with remodeling suppressants like estrogen, risendronate, alendronate, and zoledronic acid and approximately one third of that seen with denosumab (16).

Suppression of remodeling is associated with a BMD increase of approximately 1 to 3% (17). Shea *et al.* reported a meta-analysis of 15 trials in which 1806 postmenopausal women were randomized to calcium supplementation or usual calcium intake over 2 to 4 yr (17). The pooled BMD difference was approximately 1.5 to 2% relative to controls (Figure 2). Changes in the supplemented group relative to baseline are likely to be less if patients in the control group lose bone. This is important if a BMD change in an individual (relative to baseline, not control values) is a surrogate for a change in absolute fracture risk, as is often assumed.

In one of the most rigorous meta-analyses, which involved 23 trials ($n = 41,419$), calcium supplementation with or without

vitamin D was associated with a difference in BMD of 0.54% at the hip and 1.19% in the spine relative to controls ($P < 0.0001$ for both) (18). These figures were interpreted to reflect a “reduced rate of bone loss.” However, they are the result of (1) the increase in BMD produced by a reduction in the transient remodeling space deficit that occurred in the supplemented group (but not in the control), and (2) any subsequent slow down in the rate of loss when steady state is restored at the new lower remodeling rate. The relative contribution of each is uncertain. In studies of 1- to 2-yr duration, the former will dominate; in long-term studies, a reduced rate of bone loss (if it occurs) will make an increasing contribution to the overall loss of bone (described below).

The initial BMD rise of 1 to 3% is modest because suppression of remodeling is modest. Most (70 to 90%) of the new remodeling units appearing without a supplement continue to do so during supplementation because remodeling is only suppressed by 10 to 30%. This initial increase in BMD produced by partial filling of resorptive cavities present before calcium was given is blunted by the appearance of 70 to 90% of new remodeling sites simultaneously excavated despite supplementation. So the net increase in BMD is minimal. By contrast, a potent remodeling suppressant like denosumab inhibits 70 to 90% of new BMUs, so the rise in BMD is minimally blunted by the simultaneous appearance of only 10 to 30% of BMUs that remain unsuppressed (16).

Thus, the initial increase in BMD produced by a remodeling suppressant depends on its potency to suppress remodeling and the baseline remodeling rate. The latter is more significant because differences in BMD gains achieved with various doses of the same antiresorptive are trivial compared with differences produced by the same dose of an antiresorptive in individuals with different baseline remodeling (19). This is easily seen by comparing the small differences in BMD observed in the dose-finding studies of alendronate or other antiresorptives (19).

It is common for there to be no initial rise in BMD when calcium is administered. This is supported by examination of the pattern of change in BMD in the placebo (and calcium-supplemented) arm in clinical trials in postmenopausal women (20). When baseline remodeling is high, the modest reduction in the remodeling transient responsible for increasing the BMD is probably overwhelmed by the continued birth rate of most of the BMUs. No increment in BMD is observed at sites that are predominantly cortical in composition because remodeling is slow, so the remodeling space deficit is small. Minor decreases in an already small remodeling space are likely undetectable.

Figure 3A shows the differing patterns of change in BMD reported by Reid *et al.* (21). Increments in BMD were found at trabecular sites, but not at cortical sites where calcium-mediated suppression of an already slow remodeling rate may not be discernable. Nevertheless, in each of these sites, the calcium-supplemented group fared better than the control arm. When patients in the control group lost bone, remained unchanged, or had an increase in BMD, the supplemented group lost less, gained, or gained more, respectively, depending on the region studied.

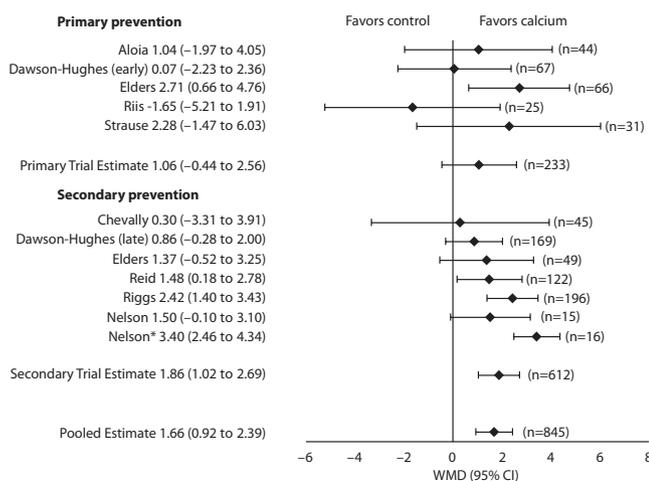


Figure 2. Meta-analysis by Shea *et al.* of antifracture efficacy studies in trials of postmenopausal women randomized to calcium supplementation or usual calcium intake. Results do not support fracture risk reduction in the lumbar spine. Pooled BMD difference after treatment with calcium compared with controls was approximately 1.5 to 2%. *Exercise arm of Nelson trial. CI, confidence interval; WMD, weighted mean difference.

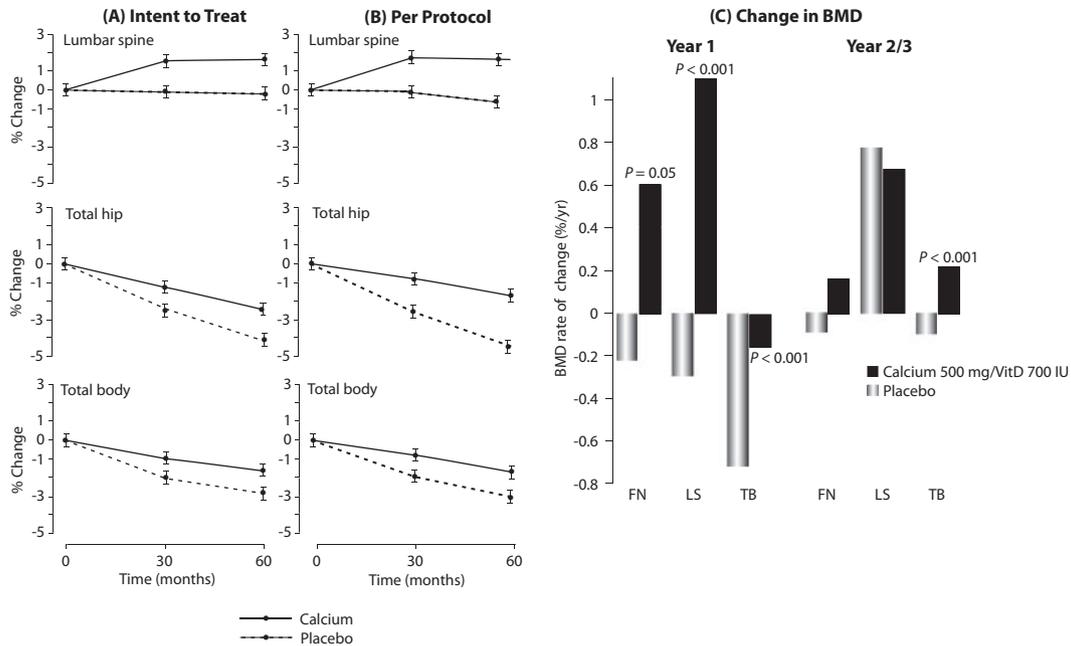


Figure 3. Calcium supplementation increased BMD at the spine but not at cortical sites. (A) Intent-to-treat analysis over 5 yr showed no between-group difference in BMD change during the last 30 mo. (B) Per-protocol analysis indicated that between-group changes differ in the total hip during the last 30 mo, which may be driven by a greater decline in placebo, a lesser decline in the supplemented group, or both. Adapted from Reid *et al.* (21). (C) BMD was higher in the supplemented postmenopausal women *versus* the control groups during the first but not second year, consistent with a reduction in the remodeling space deficit. FN, femoral neck; LS, lumbar spine; TB, total body. Adapted from Dawson-Hughes *et al.* (12).

Long-Term Calcium Supplementation: Steady State at a Lower Remodeling Rate

It is unclear whether long-term calcium supplementation increases BMD further, maintains it, or if bone loss resumes at a slower or similar rate relative to any increment of 1 to 3% achieved acutely. Of these alternatives, resumption of bone loss at a slower rate than before repletion is the most likely. Confirming this experimentally is difficult because of problems in methodology; the differences in rates of loss will be small (10 to 30% less than in controls in whom the annual rate of bone loss may be only 1%); and if calcium deficiency is modest, the effect will be even less. If dropouts occur, as is commonly the case, observations become difficult to interpret; real differences may be obscured or exaggerated depending on the errors introduced. The rate of loss will be slower if BMU imbalance is also made less negative (*i.e.*, if the supplement reduces the volume of bone resorbed and/or increases the volume of bone formed via the effects of PTH on cellular lifespan).

The question of whether rates of loss differ from controls after steady state is achieved is also burdened by analytical problems. Bone loss is assumed to be slowed because BMD is higher in the supplemented group compared with the control group. To test the hypothesis that calcium supplementation slows the rate of bone loss during the intermediate to long-term time span, the slopes in the placebo and supplemented groups should be compared after steady state is restored; however, this analysis is rarely carried out. If rates of loss were reduced by 10 to 20%, this small difference would be difficult to detect (*e.g.*,

1% in controls *versus* 0.8% in the treated group) given the precision of the method and common problems in long-term studies (*e.g.*, loss of participants and poor adherence to treatment). Difficulties are compounded if the control group is calcium-replete and/or suffers no bone loss. If the control group has no bone loss, it is not possible to infer that a lack of bone loss in the supplemented group is due to calcium supplementation; the meaning of the absence of bone loss in this supplemented group is not clear.

Thus, interpreting a reported no change, gain, or loss in BMD during long-term studies of calcium supplementation is fraught with difficulties, and the methodological aspects of each study cannot be ignored but often are in meta-analyses. Thus, findings in most studies may be due to the effects of the supplement or from inherent flaws in design and execution that are present in virtually all studies performed to date.

These problems are illustrated in one of the longest studies of calcium supplementation ever undertaken. Reid *et al.* examined the long-term effects of supplementation on BMD and fracture incidence. In this 5-yr randomized, placebo-controlled study, 1471 postmenopausal women were administered calcium 800 mg/d (21). In the intent-to-treat analysis, there were no significant differences in the rate of bone loss for supplementation and control groups during months 30 to 60 (Figure 3A). Therefore, the difference between the two groups was largely, if not entirely, explained by an increase in BMD produced during acute supplementation and perturbation of steady state

mediated by shrinkage of the remodeling transient achieved during the first 30 mo of supplementation.

In the per-protocol analysis of BMD change in patients who were compliant with treatment, there was a difference in the rate of decline in bone loss at some sites due to slowing in the supplemented group (the desired effect), accelerated loss in compliers to placebo, or both (Figure 3B) (21). Because per-protocol analysis violates randomization, the reason that rates of loss are faster or slower may have nothing to do with the calcium supplement; this possibility cannot be discounted.

Likewise, Dawson-Hughes *et al.* reported a difference in the change in BMD between women and men supplemented with calcium plus vitamin D, which was observed in the first but not second or third years of treatment (Figure 3C) (12). This is consistent with the idea that changes achieved are largely the result of alterations produced in the remodeling space in the treated group. In another study by these investigators, calcium supplementation had no BMD benefit in early postmenopausal women relative to placebo (15). The modest suppressive effect of supplementation conferred little benefit because of the high remodeling state. There was a benefit in slowing bone loss at the appendicular skeleton in women 5 yr after menopause, but only in the group with an intake <400 mg daily.

Thus, because of the lack of calcium-deplete control groups, high dropout rates, poor compliance, imprecision of the measurement method, failure to measure the slope of the regression of BMD on time, and lack of detectable bone loss in the control group, it is not certain if long-term bone loss is prevented by calcium supplements.

Calcium Supplementation and Bone Morphology

Reducing remodeling intensity may reduce fracture risk by lowering stress concentrators (as the excavated cavity partially refills), and by reducing the appearance of new stress concentrators (22,23). Although remodeling continues in the supplemented group only slightly more slowly than in controls, decay proceeds at a marginally slower rate. Thus, trabecular thinning or perforation, cortical thinning, and porosity will continue, but less so than in the control group.

If remodeling is suppressed by 10%, continued remodeling at 90% of the control rate will have trivial and undetectable effects. If supplementation suppresses remodeling by 30%, there may be a more substantial benefit if the remodeling rate is high, but if baseline remodeling is low a further reduction is unlikely to be detectable or beneficial. Further benefits may result if calcium supplementation also reduces the volume of bone resorbed and increases the volume of bone formed by each BMU. Data concerning the effects of supplementation on the basis of individual differences in baseline remodeling rate are lacking. There are no published studies reporting preservation of cortical thickness and area, reduced intracortical porosity, preservation of trabecular number or thickness, or effects on matrix composition (tissue mineralization density or collagen crosslinking).

Calcium Supplementation: Fracture Risk Reduction

No single study has credibly demonstrated a reduction in vertebral, nonvertebral, or hip fracture incidence with calcium supplementation. Although investigators make inferences regarding antifracture efficacy, these are easily challenged on the basis of flaws in study design (*e.g.*, absence of calcium-deficient subjects), execution (dropouts and poor compliance), and analysis (finding reduced fracture rates in *post hoc* analysis that may violate randomization). Randomization ensures that the prevalence of covariates that may influence outcome is equal in the two groups. This cannot be ensured when subgroups are compared or in per-protocol analyses of compliers to therapy.

Evidence that calcium supplementation reduces the risk of vertebral, nonvertebral, or hip fracture is derived from meta-analyses of these problematic trials. But even the meta-analyses provide inconsistent information, and several suggest that hip fracture rates are increased in the calcium-supplemented groups. These observations also lack credibility because of issues in trial design and execution. For example, Shea *et al.* reported fracture outcomes in five studies that included 576 women (Figure 4) (17). Meta-analysis showed a “nonsignificant trend” toward reduction in vertebral fractures in the calcium-treated group [relative risk (RR) of fracture 0.77, 95% confidence interval (CI) 0.54 to 1.09; *P* = 0.14]. The two trials reporting nonvertebral fractures had a risk reduction of 14%, with a wide CI around the estimate (RR 0.86, 95% CI 0.43 to 1.72; NS). The authors concluded that calcium supplementation showed a

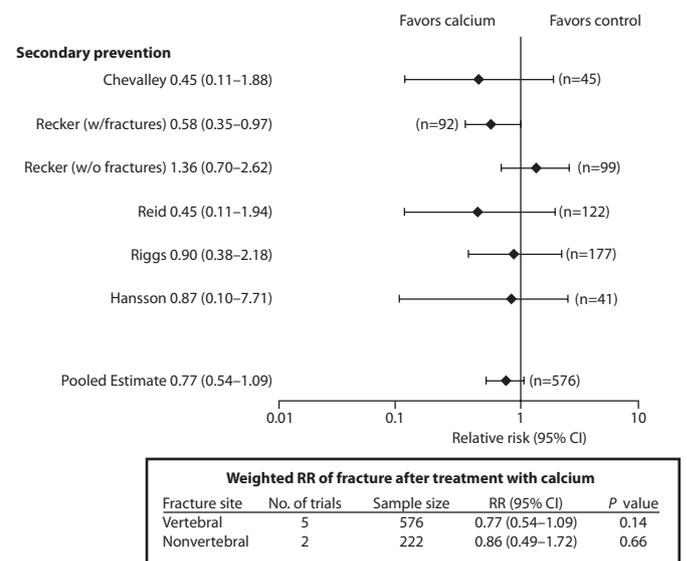


Figure 4. Meta-analysis by Shea *et al.* of antifracture efficacy studies in trials of postmenopausal women randomized to calcium supplementation or usual calcium intake. Results do not support fracture risk reduction in either vertebral or nonvertebral fractures. Figure: RR of vertebral fracture after treatment with calcium. Box: A NS trend toward reduction in vertebral fractures in the calcium-treated group was seen in five trials reporting vertebral fractures as outcomes; similar results were noted in two trials reporting nonvertebral fractures (17).

trend toward reduction in vertebral fractures but stated that the data could not meaningfully address the effect of calcium on nonvertebral fractures.

Figure 5 shows the meta-analysis results of Tang *et al.* (18), which is based on 17 trials ($n = 52,625$). Calcium supplementation with or without vitamin D was associated with a 12% risk reduction in fractures of all types (RR 0.88, 95% CI 0.83 to 0.95; $P = 0.0004$). The fracture risk reduction was 24% in trials in which the compliance rate was $\geq 80\%$ (RR 0.78, 95% CI 0.67 to 0.86; $P < 0.0001$) and 4% (RR 0.96, 95% CI 0.91 to 1.01; NS) when the compliance was $< 80\%$ (Figure 6A).

In the ten studies of calcium supplementation alone, relative fracture risk reduction (for all fractures) was 90% (95% CI 0.80 to 1.00; NS), and in the eight studies reporting on the combination of calcium plus vitamin D, the risk reduction was 87% (95% CI 0.77 to 0.97) (Figure 6B). Although it is tempting to infer that the combination of calcium plus vitamin D is better than calcium alone, the estimates of risk reduction by Tang's meta-analysis (18) did not differ from each other. In addition, of the eight studies examining calcium/vitamin D, two were in the residential care setting. Proper evaluation of the hypothesis that a combination of calcium plus vitamin D is more efficacious than calcium monotherapy requires a randomized trial. The treatment effect was also greater in participants whose daily calcium intake was low (defined as < 700 mg/d; RR 0.80 *versus* 0.95; $P = 0.008$). Risk reduction was 20% with ≥ 1200 mg calcium and 6% with doses < 1200 mg (RR 0.80 *versus* 0.94, respectively; $P = 0.006$).

The above data refer to all fractures. The reduction in hip fractures was significant [$n = 51,935$; hazard ratio (HR) 0.87, 95% CI 0.75 to 0.99] but the reduction in vertebral fractures ($n = 45,184$; HR 0.87, 95% CI 0.75 to 1.01) did not achieve statistical significance (18). Nonvertebral fracture risk was not assessed. Although absence of evidence is not evidence of absence, these

problems in study design, execution, and analysis create difficulties in making inferences with any level of confidence.

Calcium Supplementation: Is It Harmful?

Reid *et al.* reported that calcium monotherapy was associated with a 50% increased risk of hip fracture (23). Although no single study was associated with an increase in hip fracture risk, meta-analysis of the three studies demonstrated a 50% increase in risk (RR 1.50, 95% CI 1.06 to 2.12) (Figure 7). The Study of Osteoporotic Fractures showed a similar increase in hip fracture risk with calcium use (24).

Bolland *et al.* studied the association between calcium supplementation and myocardial infarction (MI), stroke, and sudden death in healthy postmenopausal women randomized to calcium supplementation ($n = 732$) or placebo ($n = 739$) (25). MI occurred more often in the calcium group *versus* the control group (45 events in 31 women *versus* 19 events in 14 women, respectively; $P = 0.01$), which was confirmed after adjudication (RR = 2.12, 95% CI 1.01 to 4.47) (Figure 8). A composite end point (MI, stroke, or sudden death) was more common in the calcium group *versus* the control group (101 events in 69 women *versus* 54 events in 42 women, respectively; $P = 0.008$).

In the Women's Health Initiative, Hsia *et al.* randomized 36,282 postmenopausal women to 500 mg calcium carbonate with 200 IU vitamin D twice daily or to placebo (26). During 7 yr, MI or coronary heart disease-related death was confirmed in 499 women assigned to calcium/vitamin D and 475 women who received placebo (HR 1.04, 95% CI 0.92 to 1.18). The authors concluded that calcium/vitamin D supplementation neither increased nor decreased coronary or cerebrovascular events. However, no inference is possible because there was not a low-calcium-intake group in this study.

Summary and Conclusions

There are no well designed and well executed studies evaluating the antifracture efficacy and safety of calcium supplementation in a cohort rigorously selected because they are deficient in dietary calcium intake. Thus, the hypotheses that calcium deficiency increases fracture risk and that it can be reduced by calcium supplementation have not been adequately tested. Antifracture efficacy was not detected in studies carried out in groups with a mean intake of approximately 800 mg/d. The null findings are not interpretable because, overall, the cohorts were not calcium-deficient, dropout rates were high, and adherence to treatment was poor. *Post hoc* analyses of subgroups with a low calcium intake or low proportion of compliers report a fracture risk reduction, but these observations are only hypothesis-generating. Findings of deleterious effects of calcium supplementation (*e.g.*, higher rates of hip fracture and cardiac events) are also only hypothesis-generating and cannot be accepted as credible evidence of adverse events.

Studies are needed in cohorts of women and men who are stratified by a dietary calcium intake above and below 500 to 750 mg/d, so that the mean daily intake is approximately 300 mg for the deficient group and approximately 1000 mg for the replete group. This design establishes the risk for fracture

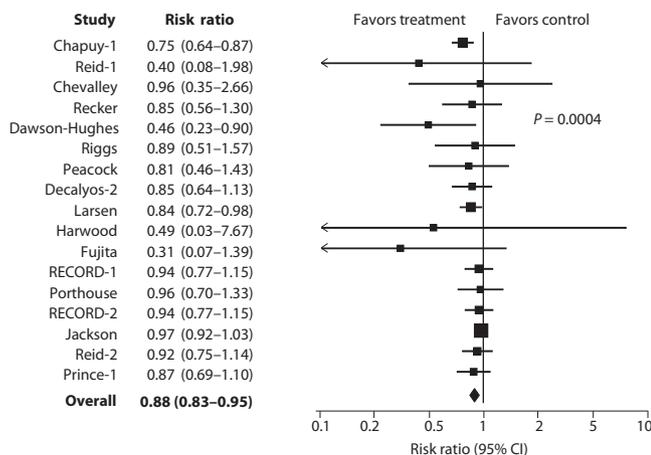


Figure 5. Meta-analysis of Tang *et al.* of 17 trials in which patients ($n = 52,625$) aged ≥ 50 yr were randomized to supplementation with calcium or calcium/vitamin D. Calcium supplementation with or without vitamin D produced a statistically significant 12% risk reduction in net fracture for all types of fractures (18).

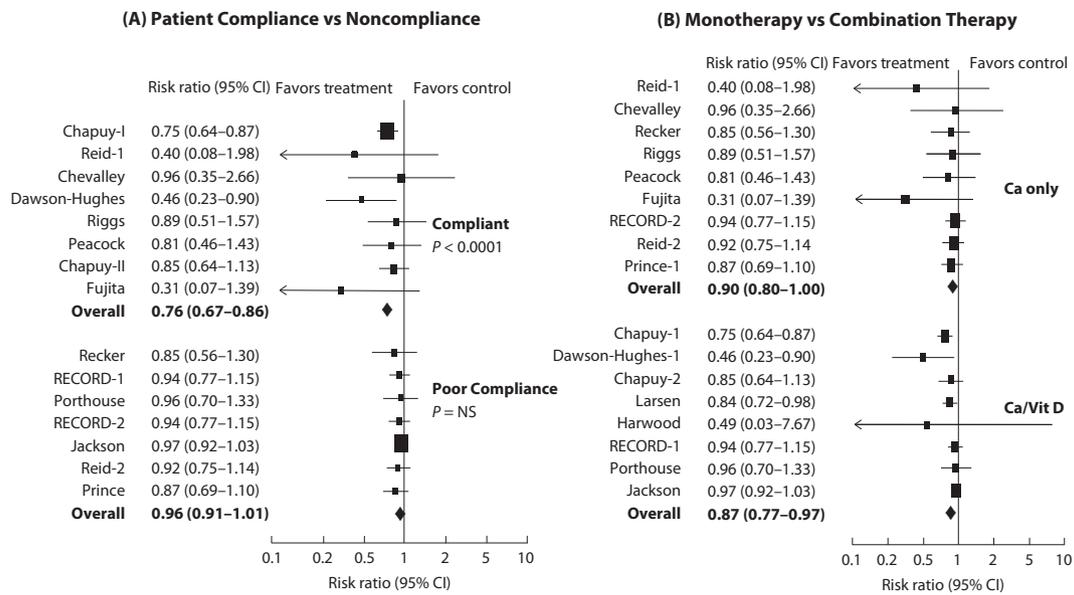


Figure 6. (A) The risk reduction for fractures was 24% in compliant subjects (compliance rate $\geq 80\%$), but no risk reduction was observed in those with poor compliance (compliance rate $< 80\%$). (B) Calcium monotherapy reduced all fractures by 10%, which does not produce a significant risk reduction in fractures. The combined effect of calcium plus vitamin D significantly reduced the risk for all fractures. Adapted from Tang *et al.* (18).

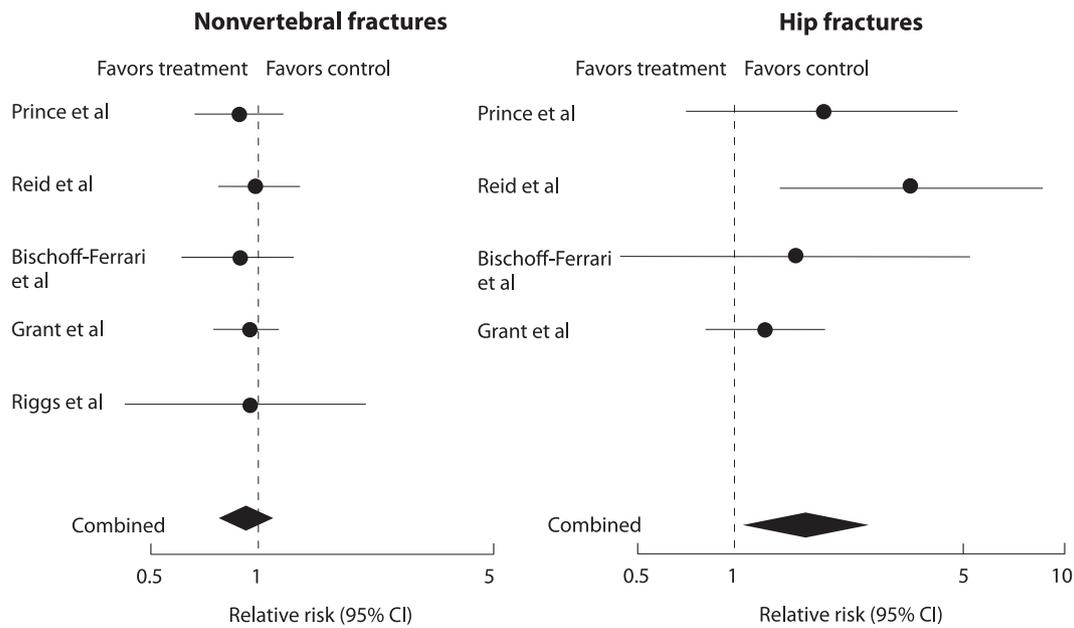


Figure 7. Meta-analysis of Reid *et al.* of four studies of trials of calcium monotherapy in women found no reduction in nonvertebral fractures and an increased risk for hip fracture. Adapted from Reid *et al.* (23).

conferred by what might reasonably be regarded as calcium “deficiency.” If each group is then randomized to calcium supplementation *versus* placebo, this design identifies any risk reduction conferred by a supplement in deficient and replete groups. A reduction in the replete group would imply that the supplement reduces the risk conferred by factors other than dietary calcium deficiency. Studies of this kind are needed in women with osteoporosis, women > 75 yr old (a cohort contributing $> 30\%$ of all fractures), women with osteopenia (be-

cause 50% of all fractures occur in this group), and men. These studies should assess specific end points such as vertebral, hip, nonvertebral, or all fractures. They must be powered to detect adverse events as well as antifracture efficacy, (*i.e.*, net morbidity and mortality), not just fracture end points.

In conclusion, consensus statements that support the widespread use of calcium are opinion-based. They accept claims of beneficial effects despite flaws in study design, execution, and analysis, and they reject reported adverse effects because

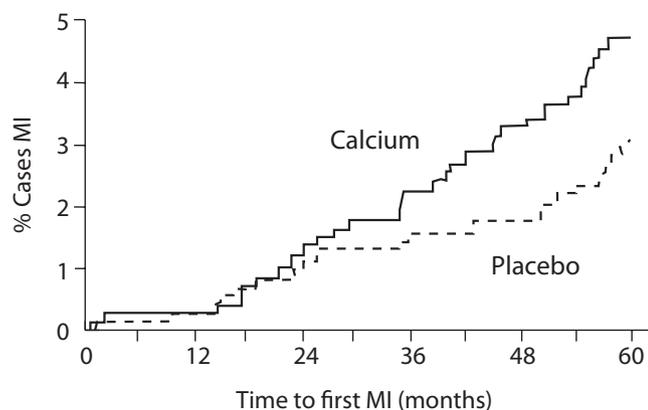


Figure 8. Calcium supplementation was associated with an increased number of cases of MI and a composite of MI, stroke, and sudden death. Table values are number of women (number of events). TIA, transient ischemic attack (25).

of them. The view that administering a placebo to a calcium-deficient group is unethical begs the question. It is unethical to do otherwise, given the possibility that calcium supplementation may do harm. Meta-analyses of these poorly designed, executed, and analyzed studies support a 10 to 15% fracture risk reduction and adverse outcomes, but they lack credibility. On the basis of current data, the widespread use of calcium supplementation in the community cannot be recommended.

Acknowledgments

This work was supported by Genzyme Corporation.

Disclosures

E.S. is a medical advisory board member and serves on the speakers bureau for Amgen, Merck Sharp, and Dome, Novartis, Proctor and Gamble, Sanofi Aventis, and Servier.

References

- Siris ES, Chen YT, Abbott TA, Barrett-Connor E, Miller PD, Wehren LE, Berger ML: Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med* 164: 1108–1112, 2004
- Johnell O, Kanis JA: An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 17: 1726–1733, 2006
- Ray NF, Chan JK, Thamer M, Melton LJ III: Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: Report from the National Osteoporosis Foundation. *J Bone Miner Res* 12: 24–35, 1997
- Rose G: Sick individuals and sick populations. *Int J Epidemiol* 14: 32–38, 1985
- Curb JD, McTiernan A, Heckbert SR, Kooperberg C, Stanford J, Nevitt M, Johnson KC, Proulx-Burns L, Pastore L, Criqui M, Daugherty S: Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol* 13: S122–S128, 2003
- Kanis JA, Passmore R: Calcium supplementation of the diet—I. *BMJ* 298: 137–140, 1989
- Kanis JA, Passmore R: Calcium supplementation of the diet—II. *BMJ* 298: 205–208, 1989
- Nordin BE, Heaney RP: Calcium supplementation of the diet: Justified by present evidence. *BMJ* 300: 1056–1060, 1990
- Nordin BE: Calcium and osteoporosis. *Nutrition* 13: 664–686, 1997
- McKane WR, Khosla S, Egan KS, Robins SP, Burritt MF, Riggs BL: Role of calcium intake in modulating age-related increases in parathyroid function and bone resorption. *J Clin Endocrinol Metab* 81: 1699–1703, 1996
- Parfitt AM: Morphologic basis of bone mineral measurements: Transient and steady state effects of treatment in osteoporosis. *Miner Electrolyte Metab* 4: 273–287, 1983
- Dawson-Hughes B, Harris SS, Krall EA, Dallal GE: Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 337: 670–676, 1997
- Prestwood KM, Pannullo AM, Kenny AM, Pilbeam CC, Raisz LG: The effect of a short course of calcium and vitamin D on bone turnover in older women. *Osteoporos Int* 6: 314–319, 1996
- Manolagas SC: Birth and death of bone cells: Basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. *Endocr Rev* 21: 115–137, 2000
- Dawson-Hughes B, Dallal GE, Krall EA, Sadowski L, Sahyoun N, Tannenbaum S: A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N Engl J Med* 323: 878–883, 1990
- Miller PD, Bolognese MA, Lewiecki EM, McClung MR, Ding B, Austin M, Liu Y, San Martin J, Amg Bone Loss Study G: Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: A randomized blinded phase 2 clinical trial. *Bone* 43: 222–229, 2008
- Shea B, Wells G, Cranney A, Zytaruk N, Robinson V, Griffith L, Ortiz Z, Peterson J, Adachi J, Tugwell P, Guyatt G: Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. *Endocr Rev* 23: 552–559, 2002
- Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A: Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: A meta-analysis. *Lancet* 370: 657–666, 2007
- Seeman E: Is a change in bone mineral density a sensitive and specific surrogate of anti-fracture efficacy?. *Bone* 41: 308–317, 2007
- Delmas PD: Treatment of postmenopausal osteoporosis. *Lancet* 359: 2018–2026, 2002
- Reid IR, Mason B, Horne A, Ames R, Reid HE, Bava U, Bolland MJ, Gamble GD: Randomized controlled trial of calcium in healthy older women. *Am J Med* 119: 777–785, 2006
- Hernandez CJ, Gupta A, Keaveny TM: A biomechanical analysis of the effects of resorption cavities on cancellous bone strength. *J Bone Miner Res* 21: 1248–1255, 2006
- Reid IR, Bolland MJ, Grey A: Effect of calcium supplementation on hip fractures. *Osteoporos Int* 19: 1119–1123, 2008

24. Cumming RG, Cummings SR, Nevitt MC, Scott J, Ensrud KE, Vogt TM, Fox K: Calcium intake and fracture risk: Results from the study of osteoporotic fractures. *Am J Epidemiol* 145: 926–934, 1997
25. Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, Gamble GD, Grey A, Reid IR: Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ* 336: 262–266, 2008
26. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, Heckbert SR, Johnson KC, Manson JE, Sidney S, Trevisan M: Calcium/vitamin D supplementation and cardiovascular events. *Circulation* 115: 846–854, 2007