Review

Calcium supplementation: Balancing the cardiovascular risks

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Abstract

Calcium supplementation has been widely accepted as a key strategy in the prevention and treatment of osteoporosis. Its role has been undermined, to some extent, by its disappointing effects on fracture in randomised controlled trials, but its use has continued to be encouraged on the grounds that it is physiologically appealing, and is unlikely to cause harm. The latter assumption is now under threat from accumulating evidence that calcium supplement use is associated with an increased risk of myocardial infarction and, possibly, stroke. The latest data, based on meta-analysis of trials involving 29,000 participants, indicate that this risk is not mitigated by co-administration of vitamin D, and that the number of cardiovascular events caused is likely to be greater than the number of fractures prevented. These findings indicate that calcium supplementation probably does not have a role as a routine preventative agent and that dietary advice is the appropriate way to attain an adequate calcium intake in most situations. Patients at high risk of fracture need to take interventions of proven anti-fracture efficacy. Available evidence suggests that this efficacy is not dependent on the co-administration of calcium supplements.

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1. Introduction

Calcium supplements have been regarded as a cornerstone of the prevention and treatment of osteoporosis, over the last 50 years. Calcium supplements have been promoted on the grounds that calcium is a major constituent of the skeleton, so more calcium should lead to a stronger skeleton. This paradigm treats the skeleton as being akin to a stalagmite in a limestone cave, expected to grow more rapidly if we drip more calcium-rich fluid onto it. This ignores the reality that bone is a collagen-based connective tissue and that bone mass is determined by the balance between the activity of the bone forming cells (osteoblasts) and that of bone resorbing osteoclasts. While substrate deficiency would be expected to have a negative impact on bone mass, oversupply of calcium should not, ipso facto, be expected to increase the bone mass.

In the last 20 years a solid evidence base has been built describing the skeletal effects of calcium, both through bone density measurements and through assessments of fracture risk. While beneficial effects have been found, they have been relatively modest, and low compliance has been a consistent feature of the large scale studies of calcium supplementation. Many physicians have continued to encourage calcium use on the grounds that it should be beneficial and there is no reason to think it does any harm. The lat-
ter assumption is now called into doubt by accumulating evidence that calcium supplement use increases the risk of cardiovascular disease. This suggestion requires that we carefully consider the balance of risk and benefit with calcium supplement use, as we would with any pharmaceutical intervention.

2. How important is calcium for bone health?

Very low calcium intakes have been associated with impaired mineralisation of the skeleton because the critical calcium-phosphate product is not reached adjacent to the mineralising osteoid [1]. However, most studies have shown remarkably little correlation between dietary calcium intake and either bone density [2–4] or fracture rates [5,6] (Fig. 1). Indeed, some of the lowest fracture rates internationally are observed in Africa and Asia, where dietary calcium intakes of 300 mg/day or less are commonplace, suggesting that genetic and other lifestyle influences play a much more important role in skeletal health.

There is now a large body of data from randomised, controlled trials that mainly assesses the value of calcium supplements, since trialling food interventions is more challenging and not able to be blinded. Most of these studies have assessed an intervention of about 1000 mg/day calcium, and most have shown that this has small but statistically significant beneficial effects on bone density [7]. For example, our recent assessment of 1 g/day compared with placebo over five years, showed a reduction in the rate of bone loss at the total hip of 36% in the intention-to-treat analysis, and 68% in the per protocol analysis [8]. The difference between these two analyses highlights a major problem with calcium supplements—that of compliance. In spite of these highly significant effects on bone loss, this study did not provide consistent evidence of anti-fracture efficacy, and this has been the general finding [7]. Most large studies show small beneficial trends in fracture risk, with the exception of the Chapuy study [9], which showed substantial reduction in total fracture numbers. This trial used an intervention of calcium plus vitamin D in a population of institutionalized elderly women, markedly deficient in both. Meta-analyses of trials of calcium alone, or calcium and vitamin D co-administration, suggest that the relative risk of any fracture is reduced by 10–13% [7,10].

However, meta-analysis of trials of calcium supplements show a significant increase in hip fracture risk in those randomised to calcium alone, though a decrease from the use of calcium plus vitamin D (again dominated by the Chapuy study), and no effect overall [5,11,12]. Since hip fractures contribute the greatest morbidity and cost of any osteoporotic fracture, and since they are also associated with a substantial increase in mortality, the failure of calcium supplementation to reduce this fracture type represents a critical issue. Thus, it is not clearly established that calcium supplements as monotherapy produce a clinically significant benefit to the skeleton, since their effects on total fracture numbers are marginal and their effect on the most important fracture have not been demonstrated.

The Tang meta-analysis also documented the frequency of poor compliance with calcium supplements, most trials having a compliance of <60%. There was no reduction in fracture risk in trials with poor compliance (relative risk 0.96 [0.91–1.01]). This problem of compliance is probably related to the size of calcium tablets and to the gastrointestinal side-effects associated with their use [8]. Because of this, it is important to consider the effects of smaller doses of calcium on bone density, since this is often what patients will be receiving, whatever is prescribed. We have recently examined this in men and found no hint of a bone density benefit from the use of 600 mg/day of calcium, in contrast to a clear beneficial effect from twice that dose [13] (Fig. 2). Dawson-Hughes studied a calcium dose of 500 mg/day and found that this was effective in men, but not in women [14]. The possibility of substantially lower efficacy with lower supplement doses, and the difficulty the trial subjects have in sustaining regular supplement intakes long-term, might account for the disappointing anti-fracture efficacy of this intervention. Calcium is an anti-resorptive of lower potency than raloxifene [15], and it effect on non-vertebral fractures is entirely consistent with this.

3. Calcium supplement effects on vascular endpoints

3.1. Calcium monotherapy

During the period that trials have been undertaken to determine the skeletal effects of calcium supplements, there has also been interest in the possibility that calcium supplements might have an impact on vascular disease. The outcome most frequently studied is blood pressure, where a consistent body of evidence has developed showing small reductions in both systolic and diastolic pressures from the introduction of calcium supplements [16–18]. There have also been reports that calcium supplements either reduce total cholesterol or have a beneficial effect on the HDL/LDL cholesterol ratio [19,20]. These trial findings, together with observational data showing reduced cardiovascular mortality in hard water areas [21] and in individuals with high calcium intakes [22,23] prompted us to pre-specify myocardial infarction and stroke as secondary endpoints in the Auckland Calcium Study, a randomised, controlled trial of 1500 postmenopausal women over five years. Contrary to our hypothesis, we found increases in both these events, which were significant for self-reported myocardial infarction (relative risk 2.12, 95% confidence interval [CI] 1.01, 4.47) [24]. Because of the potential significance of this finding, all myocardial infarction, stroke and sudden death events, including additional events identified after a search of the national database of hospital admissions, were adjudicated by physicians blinded to treatment allocation. After adjudication, the relative risk of myocardial infarction in the calcium group was 1.49 (0.86, 2.57), rate ratio 1.67 (0.98, 2.87). The rate ratio for the composite of myocardial infarction, stroke and sudden death was 1.43 (1.01, 2.04). These data were not definitive, but provided a worrying signal of cardiovascular harm. The publication of this work in 2008 led to much controversy and, in some circles, disbelief that such a widely used intervention could have such an important, unrecognized adverse effect. Such a situation can certainly arise with a non-pharmaceutical intervention, since these agents are not subjected to the rigorous, pre-registration safety assessments. This probably represents a fault in the current system, since any biologically active agent can have off-target effects (beneficial or detrimental) and these will not be detected unless a comprehensive assessment of treatment outcomes is routinely put in place.

To determine whether the adverse cardiovascular findings from the Auckland Calcium Study were present in other trials, we undertook a meta-analysis of cardiovascular events, from all published, randomised, controlled trials of calcium supplementation [25]. Because cardiovascular events were not pre-specified endpoints of most of these studies, we used the adverse event databases to identify these events. In most trials, cardiovascular events were based on participant reports, death certificates (60% of MI, and 46% of strokes in the largest contributing trial), or records from their general practitioners, and were not formally adjudicated. This may introduce noise into the data, but because the trials were blinded and randomised, it will not introduce bias. Thus, it will mitigate against finding an adverse effect, rather than creating a spurious positive finding. Using a protocol agreed by the contributing authors prior to trial data being provided, we pooled individual
Fig. 1. Cross-sectional associations between dietary calcium intake and total hip bone mineral density (upper panel) and hip fracture risk in women. The data in the upper panel are from 4958 women aged >20 years surveyed in NHANES III, and are stratified by serum 25-hydroxyvitamin D levels. For each vitamin D category, bone density is shown for quartiles of dietary calcium intake. The lower panel shows relative risk of hip fracture according to calcium intake in a meta-analysis of prospective cohort studies involving 170,991 women. No association was apparent. Figures are from the studies of Bischoff-Ferrari et al. [3,5], used with permission.

Patient data from five trials (comprising 8151 participants) and trial-level data from 11 trials (comprising 11,921 participants, the latter figure representing 93% of all trial subjects identified from our literature search—adverse event data were not available in the remaining 7%). In the individual patient analysis, 143 people allocated to calcium had a myocardial infarction during the median follow-up time of 3.6 years, compared with 111 allocated to placebo. The hazard ratio for incident myocardial infarction as 1.31...
(95% CI, 1.02, 1.67, \( P = 0.035 \)) in those allocated to calcium. The comparable data for stroke were 167 people allocated to calcium and 143 allocated to placebo, producing a hazard ratio of 1.20 (95% CI, 0.96, 1.50, \( P = 0.11 \)). From these data it can be calculated that the number needed to treat with calcium for five years to cause one incident event was 69 for myocardial infarction, 100 for stroke, and 61 for any of myocardial infarction, stroke or sudden death. These same studies show a hazard ratio for fracture of 0.90 (95% CI, 0.80–1.01) and a number needed to treat of 39. Thus, treatment of 1000 people with calcium for five years would cause an additional 14 myocardial infarctions and 10 strokes, and prevent 26 fractures. Trial level analyses produced similar findings with a relative risk of myocardial infarction of 1.27 (95% CI, 1.01, 1.59, \( P = 0.038 \)) and that for stroke of 1.12 (95% CI, 0.92, 1.36, \( P = 0.25 \)).

Two aspects of these analyses deserve comment. The Kaplan–Meier plots for myocardial infarction show an increase in event rate in the calcium group within the first year of the study with a further divergence of the groups subsequently. In contrast, the trend towards a between-groups difference for stroke emerges only after one year. These apparent differences may give insight into the pathogenesis of the calcium effects. For instance, effects on platelet function or other aspects of coagulation, on vascular reactivity or the stability of atherosclerotic plaques could all produce an early effect, whereas acceleration of vessel wall calcification would be expected to proceed more slowly. An important point to draw from the trial level analyses is the consistency of the direction and magnitude of the adverse effects across the major trials studied, irrespective of the means by which the cardiovascular events were ascertained. Meta-analyses of controlled trials with homogeneity of outcomes are regarded as the highest level of evidence in the hierarchy of evidence-based medicine.

### 3.2. Calcium with vitamin D

The finding that calcium monotherapy increases risk of myocardial infarction prompted interest in the cardiovascular effects of calcium and vitamin D co-administration, which is commonly prescribed for skeletal health. One other study of calcium supplementation to pre-specify cardiovascular events and to adjudicate these events, is the Women’s Health Initiative (WHI). These data have been published [26] and do not appear to show adverse effects, though there is some heterogeneity in the subgroup analyses and a significant interaction between treatment allocation and BMI, such that calcium with vitamin D has a more adverse effect on vascular risk in non-obese subjects. The most obvious reason for the WHI to produce a different outcome from our meta-analysis is that a different intervention was studied—calcium with vitamin D. However, while vitamin D has been suggested to be vasculo-protective, it is not clear how it would specifically antagonise the adverse effects of calcium on blood vessels so it would be expected that individuals taking calcium with vitamin D could still be at higher vascular risk than those taking vitamin D alone. The WHI population is younger and more obese than that in our meta-analysis and both these factors could contribute to the different outcome.

A further unique feature of the WHI is that study participants were permitted to enter the study even if they were self-administering calcium supplements—at baseline 54% were. Therefore, in the majority of participants, this study assesses the effect of augmenting pre-existing calcium supplementation, rather than the effect of a de novo intervention. This represents a very unusual study design which would probably not be contemplated in the context of a pharmaceutical trial. If dietary and supplement sources of calcium have the same biological effects, and if the dose–response is linear over the range of intakes studied, such a design may be acceptable. However, it would seem important to formally test these assumptions, which can be done by testing for an interaction between self-administration of calcium supplements at study entry and the effect of treatment allocation on cardiovascular risk. We have now undertaken these analyses using a protocol approved by the National Heart Lung and Blood Institute (in the NIH) prior to the database being provided to us, and have found that there is a statistically significant interaction, such that the hazard ratio for clinical myocardial infarction is 1.22 (1.00, 1.50) in women not self-administering calcium at baseline, in contrast to a hazard ratio of 0.92 (0.75, 1.13) in those taking non-protocol supplements. There is also a significant interaction for stroke (hazard ratios 1.17 and 0.83, respectively) and for the composite of clinical myocardial infarction or stroke (hazard ratios 1.16 and 0.88, respectively), the latter data being based on 708 events in the women not taking personal calcium supplements. Thus, when the analysis of the WHI is restricted to those not self-administering calcium, it shows the same increase vascular risk as we identified in trials of calcium monotherapy. In the remainder of the study cohort, the WHI data suggest that increasing the calcium dose does not increase the vascular risk further.

The WHI is not the only study with vascular event data following randomisation to CaD or placebo—this is also available from RECORD and from a smaller US study. Accordingly, we have carried out trial level meta-analyses of these three studies to quantify the effect of CaD on both myocardial infarction and stroke, finding relative risks of 1.21 (1.01, 1.44) and 1.20 (1.00, 1.43), respectively. These results do not suggest heterogeneity between trials of calcium monotherapy and trials of CaD, so it is appropriate to pool these databases to provide a comprehensive meta-analysis of the cardiovascular effects of calcium supplementation, with or without vitamin D.

These data are shown in Fig. 3 for myocardial infarction (upper panel), and stroke (lower panel). The patient level data are drawn from 24,869 subjects who suffered 631 incident myocardial infarctions, and the trial level data from 28,072 subjects suffering 676 events. The mean follow-up times were 5.9 and 5.7 years, respectively. Again we see the early separation of the calcium and placebo groups for myocardial infarction incidents, and the data from the WHI (excluding those who were using personal calcium at randomisation) shows essentially the same results on the Forrest plot as the other major studies, whether or not vitamin D formed part of the intervention. The hazard ratio for myocardial infarction is 1.26 (1.07, 1.47, \( P = 0.005 \)), and the relative risk 1.24 (1.07, 1.45, \( P = 0.004 \)). The stroke data are comprised of 669 events from the patient level analysis and 764 from the trial level data. Again, the between-groups difference for stroke develops later than one year, though there is more heterogeneity in the Forrest plot. The hazard ratio for stroke in the individual patient analysis is 1.19 (1.02, 1.39, \( P = 0.026 \)) and the relative risk in the trial-level analysis is 1.15 (1.00, 1.32, \( P = 0.055 \)).

This larger database allows us to re-examine the balance of risk and benefit that comes from calcium with or without vitamin D. The addition of the WHI women reduces the mean age, since they were on average 10 years younger than the mean in our previous meta-analysis. Consequently, event rates are also reduced, so treating 1000 people with calcium with or without vitamin D for five years causes an additional six myocardial infarctions or strokes, and prevents three fractures. As in the older cohort, there is no net benefit from this intervention.

### 3.3. Recent studies

The size of the recent meta-analysis and the absence of major calcium trials underway at the present time, means that these findings are not going to substantially change in the next few years as a result of more data becoming available. However, several other papers published recently do merit comment.
The Western Australian group have recently published data on cardiovascular events in their RCT of calcium carbonate [27]. The self-reported data for myocardial infarction and stroke from this trial were included in our meta-analyses. Their new paper presents non-adjudicated hospital discharge data for a novel composite endpoint of 'atherosclerotic vascular mortality or first hospitalisation' which includes diagnoses as diverse as arrhythmias and heart failure. Since the concern to-date has been around myocardial infarction, and to a lesser extent stroke, the choice of this much broader endpoint will only serve to obscure any calcium effect that might be present since it includes events unlikely to be affected by the intervention. The adjusted hazard ratio for this endpoint is 0.94 with the upper end of the 95% CI extending to 1.28, which is quite consistent with the results of our meta-analyses, albeit for a more focussed endpoint. In subsequent correspondence [28] these authors have indicated that the relative risk for myocardial infarction is 1.00 (0.54–1.84) and for cerebrovascular disease excluding hemorrhagic stroke 1.10 (0.68–1.78), both results broadly consistent with the findings of our meta-analyses, but lacking the power to provide a definitive assessment of risk. The authors have not clearly explained why these data differ from the self-reported data previously published, but they have only taken the principal diagnosis from each hospital discharge record, so that vascular events occurring at the time of another illness are potentially lost. Also, further data presented in abstract form from this study indicate that calcium supplements significantly increased risk of admission to hospital with abdominal problems [29]. Whether these events overlap with the trial subjects' self-report of heart attacks, whether there were dual pathologies in some of these admissions, or whether this represents a quite independent adverse effect of calcium supplementation is unclear at the present time.

Data relevant to this issue have recently appeared as a by-product of another Australian trial which studied a sunlight + calcium intervention [30]. Six hundred and two elderly residents of aged care facilities in Sydney were randomised to receive 30–40 min of sunlight exposure daily, with or without calcium supplementation (600 mg/day), or to act as controls. Comprehensive cardiovascular adverse event data are not available from this study, but, as a result of the mean age at study entry being 86 years, death certificate data are available in 218 subjects (more than one third of the total cohort) over a mean follow-up period of 2.4 years (see Table 1). These data demonstrate an increase in all-cause mortality in the sunlight plus calcium group in comparison with the sunlight alone group. The excess mortality appeared to be principally cardiovascular. The sunlight-alone group fared rather better than the control group. This could be a chance finding, or could indicate that sunlight exposure itself is cardio-protective. These results, like those from the meta-analyses, suggest that quite short exposures to calcium supplements can produce significant changes in vascular event rates in those at high risk of vascular dis-
ease, and that effects on myocardial infarction are more profound than those on strokes.

3.4. Mechanisms of the calcium effect

The consistency of the clinical trial data throws up the challenge of explaining these surprising findings. Because of the obvious role of calcium deposition in the arterial wall in atherosclerosis, many have simply assumed that this is the product of calcium being transferred from the ingested supplement to the blood vessels. While this may be the case, other possibilities and intermediate mechanisms should be entertained. Calcium is a key cofactor in blood coagulation, and clot formation is a critical step in myocardial infarction, so subtle changes in the coaguability of blood following calcium ingestion could be involved. Blood clotting also is critically dependent on platelet function, and platelets have calcium sensing receptors, so might respond directly to changes in circulating calcium concentrations. The calcium sensing receptor is also expressed in blood vessel walls, so changes in endothelial cells or smooth muscle cells might be important. The process of arterial calcification is now recognised as being closely regulated by a number of inhibitors including pyrophosphate and fetuin-A. Increases in circulating calcium would be expected to lead to complexing of pyrophosphate, with a reduction in its capacity to inhibit vessel wall calcification. The effects of altered calcium levels on fetuin-A have not yet been explored. Much of the research carried out in this area has been in patients with renal failure where calcium supplements have been shown to increase mortality in dialysis patients [31] and also to accelerate coronary artery calcification in pre-dialysis patients whose levels of renal impairment are comparable to those commonly seen in the elderly population provided with calcium supplements for osteoporosis prevention [32]. In dialysis patients, high levels of serum calcium are associated with higher mortality [33,34] and high-calcium dialysate has been associated with increased indices of inflammation, malnutrition and increased mortality [35]. The relevance of these findings to the elderly, non-dialysed population remains to be determined.

However, there are also data in normal populations indicating that higher serum calcium levels within the normal range are associated with increased carotid plaque thickness [36], an increased likelihood of abdominal aortic calcification [37], increased risk of cardiovascular events [38–41], and increased mortality [42]. Ingestion of calcium supplements abruptly increases serum calcium for up to 6 h and the magnitude of these increases is comparable to differences in baseline serum calcium which have been found to be associated with adverse cardiovascular outcomes, in the studies just cited. Interestingly, serum calcium levels have also been shown to be associated with increased cardiovascular risk (based on glucose sensitivity and circulating lipids) in healthy adolescent Americans [43]. The increase in serum calcium following calcium supplement ingestion contrasts with the minimal effect of calcium-rich foods on serum calcium. There is a similar contrast in population data for dietary calcium intake, where high intakes are not associated with increased cardiovascular risk, and sometimes with trends in the opposite direction [44]. Thus, there is no reason, based on present evidence, to extrapolate our concern regarding the use of calcium supplements to the intake of calcium-rich foods.

4. Conclusion

The consistent message from the meta-analyses of clinical trials is that calcium supplements probably carry a small but significant adverse effect on cardiovascular risk. Their beneficial effect on fractures is also small, so it is likely that there is no net benefit from their use. This suggests that we need to look elsewhere for strategies for preventing postmenopausal bone loss. Lifestyle interventions should include smoking cessation, weight maintenance, and moderation of alcohol intake. Encouragement of dietary calcium intake is reasonable, since the balance of current evidence does not demonstrate a cardiovascular risk associated with calcium from food, although there is little compelling evidence that dietary calcium intake is associated with subsequent fracture risk. In individuals who have a fracture risk which justifies pharmaceutical intervention, then the use of bisphosphonates without calcium supplements has been shown to produce comparable changes in bone density [45,46] and fractures [47] to those found with a combined intervention of calcium and bisphosphonate.

There is an urgent need for more research to gain insight into the mechanisms of the adverse vascular effect of calcium, since this might lead to strategies for circumventing it. However, it is inappropriate to delay changes in clinical practice pending the arrival of more research data, because the current meta-analyses are based on 29,000 study participants and more than 160,000 subject-years of data, and there are few studies of calcium supplementation of any size underway at the present time. Therefore, data to be presented in the next few years will impact minimally on the currently available results.

Contributors

The article was drafted by IRR, then critically revised by the other authors.

Conflict of interests

IRR has received research support from and acted as a consultant for Fonterra and had study medications for clinical trials of calcium supplementation supplied by Mission Pharmacal. The other authors have no conflicts.
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