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Review Article

Should We Prescribe Calcium Supplements For Osteoporosis Prevention?

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Advocacy for the use of calcium supplements arose at a time when there were no other effective interventions for the prevention of osteoporosis. Their promotion was based on the belief that increasing calcium intake would increase bone formation. Our current understandings of the biology of bone suggest that this does not occur, though calcium does act as a weak antiresorptive. Thus, it slows postmenopausal bone loss but, despite this, recent meta-analyses suggest no significant prevention of fractures. In sum, there is little substantive evidence of benefit to bone health from the use of calcium supplements. Against this needs to be balanced the likelihood that calcium supplement use increases cardiovascular events, kidney stones, gastrointestinal symptoms, and admissions to hospital with acute gastrointestinal problems. Thus, the balance of risk and benefit seems to be consistently negative. As a result, current recommendations are to obtain calcium from the diet in preference to supplements. Dietary calcium intake has not been associated with the adverse effects associated with supplements, probably because calcium is provided in smaller boluses, which are absorbed more slowly since they come together with quantities of protein and fat, resulting in a slower gastric transit time. These findings suggest that calcium supplements have little role to play in the modern therapeutics of osteoporosis, which is based around the targeting of safe and effective anti-resorptive drugs to individuals demonstrated to be at increased risk of future fractures.

Key Words: Calcium, Fractures bone, Myocardial infarction, Osteoporosis

INTRODUCTION

For many decades there has been advocacy for the use of calcium supplements in the prevention and treatment of osteoporosis. In the 1960s and 1970s, this was in the context of having no proven medications for osteoporosis management, a situation which has now changed dramatically. The rationale for advocating calcium is that it is *one* of the principal constituents of bone, though it should always be remembered that bone is a connective tissue, so its fundamental framework is a protein matrix (type I collagen) which is laid down by osteoblasts (bone forming cells) and remodelled and removed by osteoclasts (bone resorbing cells). In adult life, this cell-mediated process of bone remodelling takes place at intervals across the skeletal surface, and involves the removal and replacement of small packets of bone. Once osteoblasts have laid down new type 1 collagen, calcium and phosphate crystalize between the collagen fibres, providing bone with its compressive

strength. Thus, bone balance, or the change in bone density over time, is driven by the balance of activities of bone forming cells and bone resorbing cells. Providing excess calcium and phosphate will not lead to the creation of more bone, since the amount of bone laid down is determined by the number and activity of osteoblasts. While an adequate supply of calcium and phosphate is important to ensure that bone laid down by osteoblasts is normally mineralised, an oversupply is unlikely to be helpful.

1. Calcium intake and bone

It is often assumed that higher calcium intakes result in greater bone density and fewer fractures. However, there are very few data to support this belief, and it is notable that calcium intake does not figure in any of the fracture risk calculators (e.g. fracture risk assessment tool [FRAX], Garvan) currently used. Thus, cross-sectional studies that relate customary calcium intake to bone density show no relationship between these variables (in the National Health and Nutrition Examination Survey [NHANES] the *P* value for differences in density across quintiles of calcium intake is 0.84 at the spine and 0.72 at the femoral neck [1]) and the same is true when fracture risk is related to calcium intake.[2]

Many clinical trials have now been carried out to determine whether calcium supplements can improve bone density and reduce fractures. There is consistent evidence that the use of calcium supplements reduces bone turnover by about 20%, and this is associated with a reduction in postmenopausal bone loss.[3] A study in which frail women living in institutions for the elderly were randomised to calcium plus vitamin D or to placebo demonstrated reduction in hip fracture risk [4] but such positive results are not found in studies with community dwelling individuals. Between 2005 and 2010, six large randomised controlled trials of calcium (with or without vitamin D) in community-dwelling individuals were published - none of these trials showed statistically significant fracture prevention.[3,5-8] Recent meta-analyses confirm that calcium with or without vitamin D is not effective for the prevention of vertebral fractures (odds ratio [OR] for calcium alone 0.74 [0.45, 1.12], calcium+D OR 0.99 [0.74, 1.41]), non-vertebral fractures (calcium OR 1.00 [0.82, 1.22], calcium+D OR 0.94 [0.84, 1.02] or hip fractures (Fig. 1) in community-dwelling individuals.[9,10] Therefore, the rationale for continuing to use calcium supplements for osteoporosis management is under question, and this questioning becomes even more acute when the possible side-effects of calcium supplements are considered.

2. Cardiovascular effects of calcium supplements

A number of observational studies have assessed whether there is a relationship between *dietary* calcium intake and cardiovascular health, and generally none has been found. However, randomised, controlled trials of calcium supplements have suggested beneficial effects on circulating lipid levels[11] and small decreases in blood pressure.[12,13] Because of these observations, we hypothesised that calcium supplementation might decrease the risk of cardiovascular events, and this was a pre-specified secondary endpoint in the Auckland Calcium Study. To our surprise, we found the opposite, observing a significant increase in the risk of myocardial infarction, and an upwards trend in risk of stroke.[14] In light of this, and the absence of other published data on the subject, we contacted the authors of all of the major randomised, controlled trials of calcium supplements in older adults in order to obtain cardiovascular adverse event data. The protocol for this analysis was finalised before the data were provided to us, and the analysis confirmed the adverse effect of supplements on myocardial infarction, and also demonstrated an adverse but non-significant effect of these supplements on stroke risk.[15]

The Women's Health Initiative (WHI) investigators also addressed this question in their large trial in which the intervention was calcium plus vitamin D.[16] There were adverse trends in some cardiovascular endpoints, particularly in non-obese women, though the authors concluded that no significant effect was present. The WHI differed from the trials included in our 2010 meta-analysis in that the intervention included vitamin D as well as calcium, the trial subjects were a decade younger, and more than half of them were already taking calcium supplements at the time they were randomised. We hypothesised that the high level of self-administration of calcium may have reduced the sensitivity of the study to observe an adverse effect of the supplements on cardiovascular risk, and proposed an analysis which would determine whether there was an interaction between calcium supplement use at

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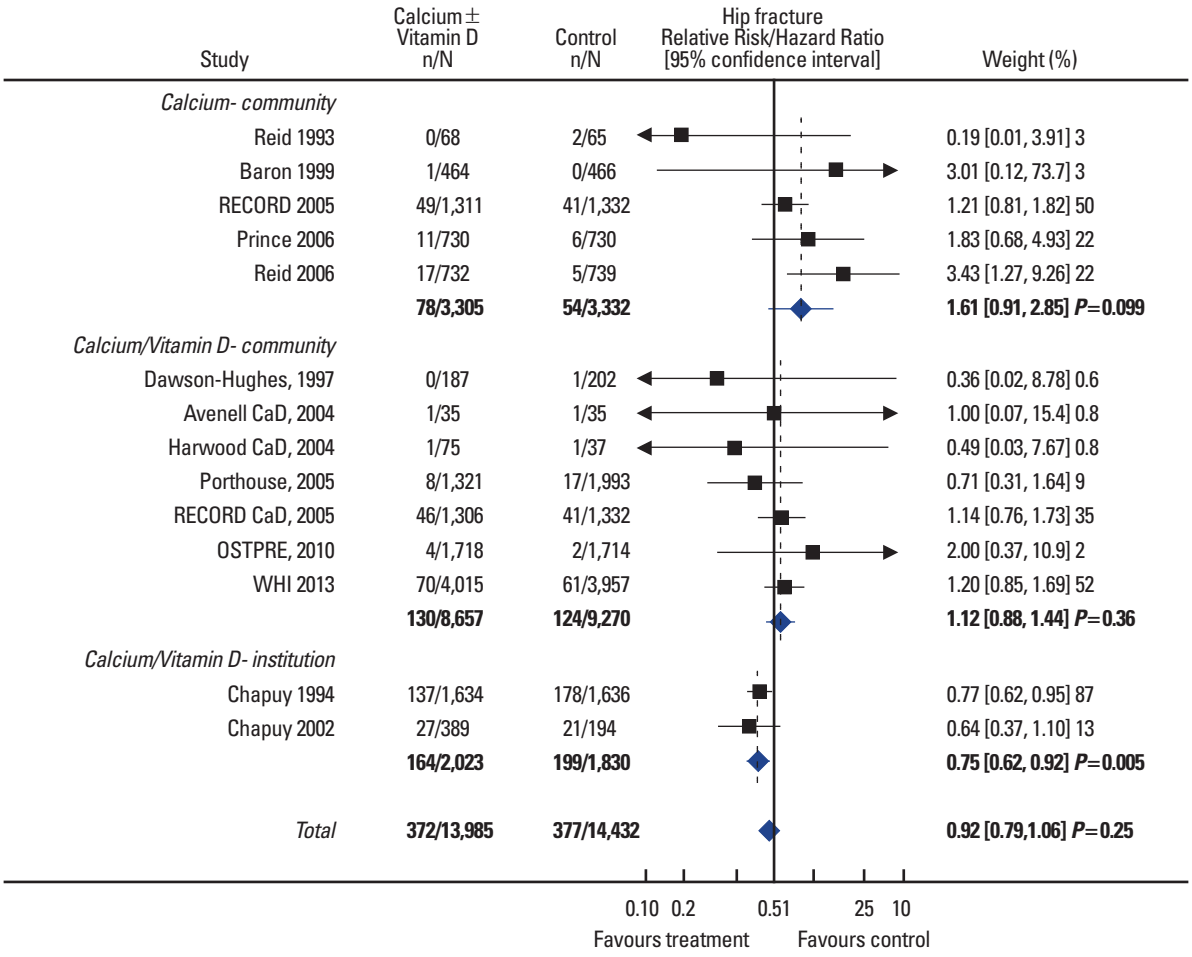

Fig. 1. Meta-analysis of the effects of calcium alone or with vitamin D, on hip fracture risk in randomised controlled trials. Studies have been divided according to the residential status of their participants. The classification of the Harwood study is debatable since subjects were in hospital following fractures at trial entry, though most had been community dwelling previously. [Reprinted from "Calcium risk–benefit updated–New WHI analyses", by Reid, IR, Bolland, MJ, 2013, Maturitas, 77(1), pp. 1-3. Copyright 2013 by the Elsevier. Reprinted with permission].

the time of randomisation in the study, and the effect of the trial intervention on cardiovascular risk. This protocol was approved by the National Institutes of Health (NIH; who held the database) before the data were provided to us. Analysis demonstrated that in calcium-naïve women there was a significant adverse effect on myocardial infarction from randomisation to calcium plus vitamin D, whereas in those already taking calcium this was not observed. [17] The difference between these groups was statistically significant. In fact, the results from the calcium-naïve subjects in the WHI mirrored very closely those from our previous meta-analysis of calcium supplements alone. In both datasets, the effects on myocardial infarction were seen within the first year of supplementation, whereas effects on stroke had a much slower onset (Fig. 2).[18] Also, the size of the adverse effects on both events was very similar in the two datasets. When the data from the calcium-naïve subjects in the WHI was combined with all other trials of calcium with or without vitamin D, a 24–26% increase in the risk of myocardial infarction and a 15–19% increase in the risk of stroke was observed, both of which were significant.[17] As a result of these findings, together with the absence of any consistent evidence that high dietary calcium intake is deleterious to cardiovascular health, it is now generally recommended that we should obtain our calcium requirement from diet, rather than from the use of supplements.[19,20]

In spite of the consistency of the data presented in Figure 2 and in the Bolland meta-analyses, controversy persists regarding the adverse cardiovascular effects of calci-

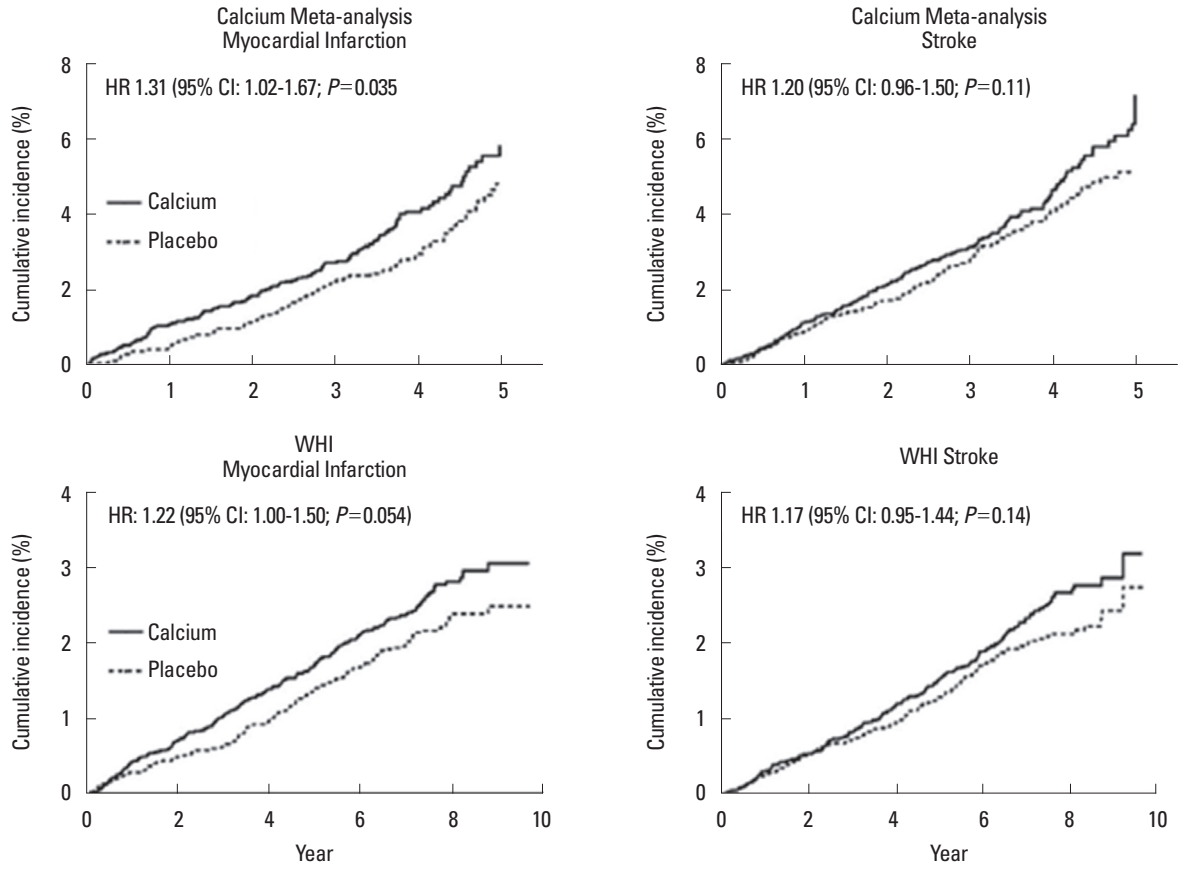

Fig. 2. Kaplan–Meier survival curves for time to incident myocardial infarction or stroke by treatment allocation in a meta-analysis of patient-level data from five trials of calcium supplements used as monotherapy (n=8,151) and in women in the Women's Health Initiative (WHI) calcium and vitamin D trial not using personal calcium supplements at randomization (n=16,718). The magnitude and time-course of the effects of calcium supplements on the two classes of vascular events were very similar in these independent databases. CI, confidence interval; HR, hazard ratio. [Reprinted from "Subgroup analysis for the risk of cardiovascular disease with calcium supplements", by Radford LT, Bolland MJ, Gamble GD, Grey A, Reid IR, 2013, Bonekey Rep, 77(1), pp. 1-3. Copyright 2013 by the Nature Publishing Group. Reprinted with permission].

um. At the 2013 American Society for Bone and Mineral Research (ASBMR) meeting, a further meta-analysis was presented which confirmed our results for the use of calcium supplements alone.[21] However, for the calcium plus vitamin D analyses, they chose to include the WHI data from those women already taking calcium supplements (even though we have demonstrated that their response to intervention is different from that of calcium-naïve women) and also data from the trial of Larsen.[22] This is a cluster randomised study (i.e. not a true randomised, controlled trial) in which uptake of the calcium plus vitamin D intervention was very low, and in which baseline cardiovascular risk was significantly different between those agreeing to take the calcium plus vitamin D intervention and those agreeing to act as control subjects. The addition of these two additional cohorts results in a relative risk of myocardial infarction of 1.09 which is no longer statistically significant, but still suggestive of an adverse effect which is greater than any benefit in terms of fracture prevention. Thus, this controversial analysis still does not provide evidence of net benefit from taking calcium supplements.

The publication of our meta-analyses has led to a large number of observational analyses assessing the relationship between calcium supplement use and cardiovascular risk. A number of positive and a number of negative analyses have resulted, reflecting the much lower power of observational studies to address such questions, and the problem of residual confounding which always makes interpretation of observational data difficult. It is noteworthy that the studies which have suggested a significant adverse effect of calcium supplements have not been balanced by a similar number of studies suggesting a significant benefit.

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Thus, on balance, the observational data are generally consistent with the randomised, controlled trial findings.

3. Trials in related areas

While there is no randomised, controlled trial of calcium supplements which has cardiovascular events as its endpoint (and neither is there likely to be), there have been several other recent studies which reinforce the suggestion that calcium supplementation may have adverse cardiovascular effects. Calcium supplements have long been used in patients with renal failure for their phosphate binding properties, including in patients not yet requiring dialysis. Jamal et al.[23] recently published a meta-analysis of trials comparing calcium-containing phosphate binders with other agents not containing calcium. She found that mortality was 22% lower in those using phosphate binders which did not contain calcium, and this meta-analysis was accompanied by an editorial entitled *The demise of calcium based phosphate binders*.[24] This suggests that in patients with renal impairment, calcium supplements have a significant adverse effect on mortality, most of this mortality being cardiovascular. Since many older patients at risk of osteoporosis have glomerular filtration rates <60 mL/minute (i.e. stage 3 chronic kidney disease [CKD]) these findings are likely to be directly applicable to the population at risk of osteoporosis.

The immediate biochemical consequence of taking a calcium supplement is an increase in circulating calcium levels, which persists for >8 hours.[25] The mirror image of these changes is produced by the infusion of a calcium chelator, such as the ethylenediaminetetraacetic acid (EDTA) infusions which are used in chelation therapy. This highly controversial intervention was recently the subject of an NIH-funded trial which demonstrated an 18% decrease in risk of cardiovascular events. This suggests that lowering serum calcium is associated with decreased cardiovascular risk, and is consistent with a large body of observational data which has shown associations of circulating calcium levels with carotid plaque thickness,[26] calcified plaque in the coronary arteries (Fig. 3),[27] cardiovascular event

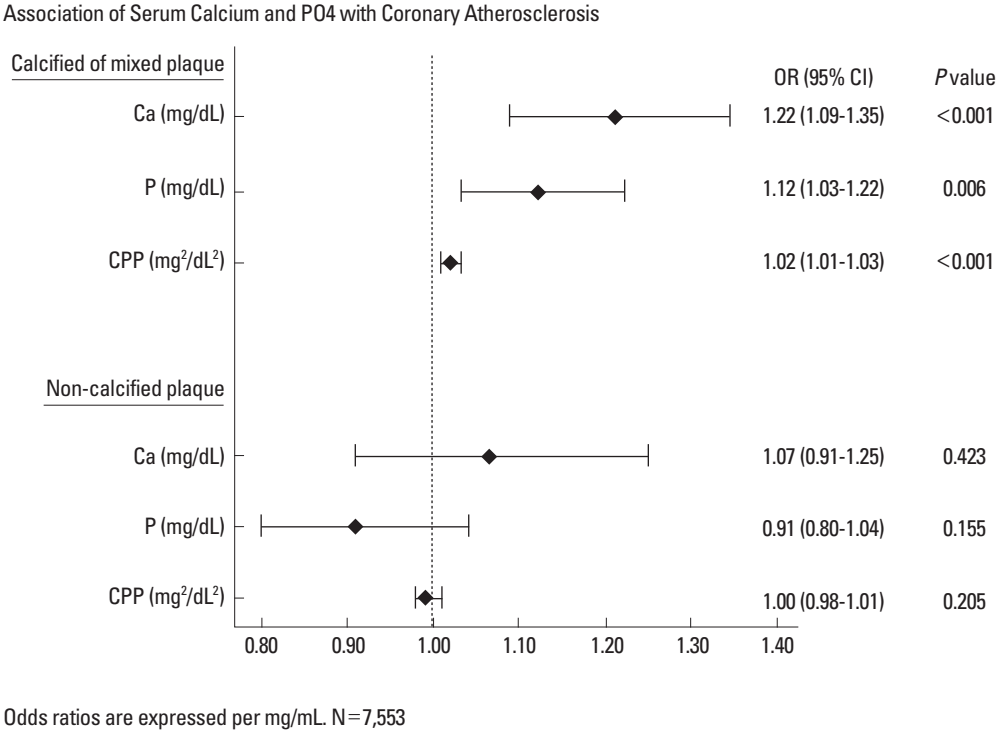

Fig. 3. The association of serum calcium, phosphate, and calcium–phosphate product (CPP) with the presence of coronary artery disease, divided into calcified or mixed plaque, and non-calcified plaque. Plaque was measured by cardiac computed tomography in 7553 Korean adults. [Reprinted from "Impact of serum calcium and phosphate on coronary atherosclerosis detected by cardiac computed tomography", by Shin S, Kim KJ, Chang HJ, Cho I, Kim YJ, Choi BW, Rhee Y, Lim SK, Yang WI, Shim CY, Ha JW, Jang Y, Chung N, 2012, Eur Heart J, 33(22), pp.2873-81. Copyright 2012 by the Oxford University Press. Reprinted with permission].

rate,[28,29] and mortality.[30] Thus, chelation therapy has the opposite effect to calcium supplementation on serum calcium levels, and this appears to be reflected in its opposite effects on cardiovascular event rates.

The third recent piece of data relates to the finding that the use of the calcimimetic ion, strontium, is associated with a 60% increase in the risk of myocardial infarction.[31] Strontium is adjacent to calcium in the periodic table, binds to the calcium receptor, displaces calcium in hydroxyapatite crystals in bone, and probably can substitute for calcium in a wide range of other biological functions. Thus, the finding that strontium increases myocardial infarction is entirely consistent with the trial data suggesting that calcium also has this effect.

4. Mechanisms of the adverse effects of calcium supplements on cardiovascular health

As discussed above, circulating calcium levels in the upper part of the normal range are associated with increased cardiovascular risk.[26-30] The use of calcium supplements increases circulating calcium levels to the upper part of the normal range or above. Therefore, these effects on circulating calcium concentrations are likely to mediate the adverse cardiovascular outcomes associated with calcium supplement use. The intermediary mechanisms remain to be determined, but the demonstration of associations between aortic, coronary artery and carotid artery calcification and circulating calcium levels suggest that direct effects on the vessel wall may be involved. Studies of vascular cells in culture, have suggested that higher calcium concentrations increase calcification of the cultures, and result in changes in levels of calcification-regulating proteins in matrix vesicles.[32] A further mechanism is suggested by our recent observation that calcium supplement use acutely increases blood coaguability (Bristow & Reid, unpublished observation). This is consistent with *in vitro* evidence that blood coagulation is critically dependent on ambient calcium levels.[33] Thus, the hypercalcemia associated with calcium supplement use may increase coaguability of the blood, thus increasing the risk of coronary artery thrombosis.

5. Other adverse effects of calcium

The WHI demonstrated a 17% increase in the risk of kidney stones associated with randomisation to calcium plus vitamin D.[8] For many years there has been a widespread awareness of the adverse gastrointestinal effects of calcium supplementation, and these agents are commonly associated with constipation and other symptoms of gastrointestinal distress. A recent clinical trial has demonstrated that the likelihood of being admitted to hospital with an acute gastrointestinal condition is doubled as a result of randomisation to calcium, and that this effect is large enough to completely abrogate any anti-fracture efficacy from the use of these agents.[34]

CONCLUSION

Advocacy for the use of calcium supplements arose at a time when there were no other effective interventions for the prevention of osteoporosis. Their promotion was based on the belief that increasing calcium intake would increase bone formation. Our current understandings of the biology of bone suggest that this is not likely to occur. There is evidence that calcium acts as a weak antiresorptive, through its suppression of parathyroid hormone secretion. This is likely to be the mechanism that contributes to the slowing of postmenopausal bone loss with the use of calcium supplements. Despite this, recent meta-analyses suggest no benefit from the use of calcium supplements in fracture prevention, and in fact there is evidence of adverse effects of calcium supplementation on hip fracture risk. In sum, there is little substantive evidence of benefit to bone health from the use of calcium supplements.

Against this needs to be balanced the likelihood that calcium supplement use increases the risk of cardiovascular events, formation of kidney stones, and gastrointestinal symptoms, including the risk of admission to hospital with acute gastrointestinal problems. Thus, the balance of risk and benefit seems to be consistently negative. As a result, most organisations providing advice regarding optimisation of bone health, recommend that individuals should obtain their calcium requirement from diet in preference to supplements. Dietary calcium intake has not been associated with the adverse effects associated with supplements, probably because calcium is provided in much less concentrated boluses, and these boluses are absorbed more slowly from the gastrointestinal tract since they come together with quantities of protein and fat, resulting in a slower gastric transit time. It is also important to note that we now have much more effective antiresorptive agents than calci-

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um supplements, which prevent fractures and are safe in long-term use. Therefore, osteoporosis prevention should centre on the quantitative assessment of fracture risk, and the targeting of appropriate fracture prevention therapies to those found to be at increased risk. As a result, calcium supplements have little role to play in the context of the modern therapeutics of osteoporosis.

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