ARTICLE

Calcium and cardiovascular risks

SUMMARY

Co-administered calcium and vitamin D supplements prevent fractures in institutionalised elderly women, but there is little evidence that the supplements, administered as monotherapies or in combination, prevent fractures in other people in the community.

Calcium and vitamin D supplements are not always necessary for bisphosphonates to be effective. Individuals at high risk for vitamin D deficiency should be treated with vitamin D supplements before zoledronic acid is prescribed.

There is little evidence that dietary calcium intake is associated with risk of fracture or cardiovascular events, so dietary calcium generally does not require close scrutiny.

Calcium supplements increase the risk of myocardial infarction by about 25% and stroke by 15–20%. The co-administration of vitamin D does not mitigate these risks. Widespread use of calcium supplements to prevent fractures is therefore no longer appropriate.

Introduction

Calcium and vitamin D supplements are commonly recommended for the treatment or prevention of osteoporosis and for patients taking bisphosphonate treatment. These strategies need to be reconsidered as recent evidence suggests that calcium supplements are only marginally effective in preventing fractures, and increase cardiovascular risk.

Skeletal benefits of calcium with or without vitamin D

In 1992 a trial reported that co-administered calcium and vitamin D significantly reduced the risk of hip and non-vertebral fracture in institutionalised elderly women with low dietary calcium intake and a very high prevalence of vitamin D deficiency.[1] However, for other people living in the community the evidence for the benefit of calcium or vitamin D supplements on fracture prevention is less clear. Meta-analyses of randomised controlled trials found that calcium supplements used as monotherapy marginally reduced the risk of total fracture,[2] but increased the risk of hip fracture[3]. Vitamin D supplements used as monotherapy had no effect on total fracture[4,5] and had no effect[5] or marginally increased[4] the risk of hip fracture. The addition of vitamin D to calcium supplements did not change these findings. Calcium with vitamin D marginally reduced the risk of total fracture[2] but did not prevent hip fractures[4,5].

There are several explanations why calcium and vitamin D prevent fractures in vitamin D deficient, frail, elderly women, but not in other people. The benefits seen in elderly women[1] may have arisen from correcting vitamin D deficiency and resulting osteomalacia, which is uncommon in younger people. Another possible explanation is that compliance with calcium supplements is poor (approximately 40–60% in randomised controlled trials[6-8]), which may reduce their effectiveness.

Are calcium and vitamin D supplements necessary when prescribing bisphosphonates?

In clinical trials of osteoporosis treatment, calcium and vitamin D supplements have routinely been co-administered. This has led to suggestions that bisphosphonates are only effective when co-prescribed with calcium and vitamin D, but other trials suggest this is incorrect.

The effects of alendronate on bone density were the same as alendronate plus calcium supplements in a two-year randomised controlled trial in women with dietary calcium intake of more than 800 mg/day.[9] The decreases in bone turnover and improvements in bone density with zoledronate were similar regardless of whether calcium and vitamin D were co-prescribed[10,11] or not[12]. Without calcium and vitamin D, clodronate decreased the risk of fractures by 20% in elderly women.[13] This evidence shows that bisphosphonates used without calcium and vitamin D effectively decrease bone turnover, improve bone density, and prevent fractures.

Co-prescribing calcium and vitamin D to patients taking bisphosphonates is probably unnecessary for most people. An important caveat is that vitamin D deficiency is common in frail elderly patients (in whom osteoporosis is also common). Infusion of zoledronic acid into patients with vitamin D deficiency can provoke significant hypocalcaemia so the deficiency should be corrected before treatment.

Mark Bolland
Senior research fellow

Andrew Grey
Associate professor

Ian Reid
Professor

Bone and Joint Research Group
Department of Medicine
University of Auckland
New Zealand

Key words
bisphosphonate, myocardial infarction, osteoporosis, stroke, vitamin D

Aust Prescr 2013;36:5–8

Cardiovascular effects of calcium supplements

The first evidence for the adverse cardiovascular effects of calcium supplements in non-uraemic patients came from our five-year randomised controlled trial of calcium monotherapy in 1471 healthy postmenopausal women. There were increases in cardiovascular event rates in the women allocated to calcium (23.3 vs 16.3 events/1000 patient-years, p=0.043), but the size of the study and number of cardiovascular events meant that the results were not definitive.[14]

Further randomised controlled trials of calcium to address the concern were not practical as the primary endpoint would be one of harm. We therefore undertook a meta-analysis of unpublished cardiovascular data from randomised controlled trials. The lead authors of five trials provided patient-level data, and trial-level data on cardiovascular events were available for 11 trials. Meta-analyses showed that calcium supplements increased the risk of myocardial infarction by approximately 30%. There were also smaller, statistically non-significant, increases in mortality, the risk of stroke and in a composite cardiovascular endpoint.[15]

Co-administered calcium and vitamin D

The findings of our meta-analysis related to calcium supplements used as monotherapy, whereas the use of calcium with vitamin D is more common in clinical practice. The Women's Health Initiative calcium and vitamin D trial, a seven-year randomised controlled trial in more than 36 000 postmenopausal women, had previously reported that calcium and vitamin D did not alter cardiovascular risk.[16] An unusual feature of this trial was that personal, non-protocol use of the trial medications was permitted. The majority of the participants were taking their own calcium supplements at randomisation. Widespread personal use of calcium in the trial might have obscured an adverse effect of calcium supplements on cardiovascular risk.

We re-analysed the data from the trial comparing the effects of calcium and vitamin D in non-users and users of personal calcium. In women who were not taking their own calcium at baseline but were allocated to take calcium and vitamin D in the trial, there were increases in the risk of cardiovascular events of similar magnitude to those in the previous meta-analysis of calcium monotherapy. However, in women who were already taking personal calcium supplements, taking calcium with vitamin D in the trial had no effect on cardiovascular risk.[17] The results suggested that the widespread use of personal calcium supplements in the Women's Health Initiative trial had obscured the adverse cardiovascular effects of calcium with vitamin D.

We then pooled the data from the women not using personal calcium supplements in the Women's Health Initiative trial with all other randomised controlled trials of calcium with vitamin D for which cardiovascular data were available. In this analysis, calcium with vitamin D increased the risk of myocardial infarction by 21% and stroke by 20%.[17]

Calcium with or without vitamin D

We pooled our two meta-analyses of calcium monotherapy and calcium with vitamin D, to determine the effect of calcium with or without vitamin D on cardiovascular risk. Calcium or calcium with vitamin D increased the risk of myocardial infarction by 25% and stroke by 15–19%. Based on these meta-analyses, in 1000 people treated for five years, calcium or calcium with vitamin D would cause six heart attacks or strokes and prevent three fractures.[17]

These findings are consistent with studies of patients with renal impairment, in whom calcium supplements accelerate vascular calcification and increase mortality, in both dialysis and pre-dialysis populations.[18-20] A more recent randomised controlled trial of sunlight exposure to raise vitamin D concentrations in Australian nursing home residents also found that the addition of calcium supplements to sunlight exposure was associated with increases in all-cause and cardiovascular mortality.[21,22]

Given the widespread use of calcium and its presumed safety, it is unsurprising that these unexpected findings have not been universally accepted, although few substantive criticisms have been raised.[23] Misclassification of other events as heart attacks was suggested as a possible explanation, but the increased risk is consistent whether events were self-reported, obtained from hospital discharges, death certificates or independently adjudicated. Others have suggested that the results are not valid because the trials were not primarily designed to assess cardiovascular events. This reasoning would make it impossible to ever detect unexpected adverse events. Others have suggested that more evidence is required before practice should be changed. However, there are no ongoing trials large enough to influence the results from the current meta-analyses, future trials are unlikely given the potential for harm from participating, and results of observational studies will not outweigh the Level 1 evidence from a systematic review of randomised controlled trials. Decisions about the use of calcium supplements must therefore be based on these current data.

Mechanisms

A cause for the increased cardiovascular risk remains unclear. The consistency of the results for calcium monotherapy and calcium and vitamin D suggests that the effect is caused by calcium supplements, and is not mitigated by the co-administration of vitamin D. One possible mechanism is that calcium supplements abruptly increase serum calcium.[24] Higher serum calcium concentrations are associated with many measures of atherosclerosis such as carotid artery plaque thickness[25] and aortic calcification.[26] They are also associated with the incidence of myocardial infarction[27-29] and mortality[30]. It is possible that the rapid increases in serum calcium after taking a calcium supplement may alter vascular calcification and other pathophysiological processes occurring at the blood vessel surface.

Should dietary calcium be recommended in place of calcium supplements?

There are no randomised controlled trials that have evaluated the effect of increasing dietary calcium on either fracture incidence or cardiovascular outcomes. Several observational studies have addressed this topic, although the interpretation of observational studies is difficult. Causality cannot be inferred, confounding is difficult to assess and control for, and the total calcium intake of people taking calcium supplements is usually much greater than the intake achieved through diet alone. With these caveats in mind, there is little evidence that levels of dietary calcium intake are associated with cardiovascular risk.[31-36] Similarly, meta-analyses of observational studies do not suggest that levels of calcium intake are associated with subsequent risk of fracture.[37]

Implications for practice

For the majority of patients, the weak effects that calcium supplements have on fracture risk are outweighed by the increased cardiovascular risk. Recommendations for the widespread use of calcium supplements are no longer appropriate and should be reconsidered.

The one population group in which there is clear evidence of fracture prevention with calcium and vitamin D is the institutionalised frail elderly with a high prevalence of vitamin D deficiency. In this population, however, there is also evidence that the addition of calcium supplements to sunlight exposure increases mortality, so the balance of harm and benefit currently remains uncertain. Routine vitamin D supplementation to prevent osteomalacia is reasonable in this group.

There is little evidence that levels of dietary calcium intake are associated with risk of fracture, and so dietary calcium intake does not require close scrutiny for most people. Patients at high risk of fracture should be encouraged to take drugs with proven efficacy in preventing vertebral and non-vertebral fractures. For bisphosphonates, calcium and vitamin D do not need to be routinely co-prescribed, although patients at high risk of vitamin D deficiency should be prescribed vitamin D supplements. ◁

Professor Reid has received research funding, speaker and consultancy fees from Novartis, Merck and Amgen.

Recommendations for the widespread use of calcium supplements are no longer appropriate and should be reconsidered

Q:

SELF-TEST QUESTIONS

True or false?

1. Calcium supplementation reduces cardiovascular risk.
2. Bisphosphonates do not work without calcium supplements.

Answers on page 35

REFERENCES

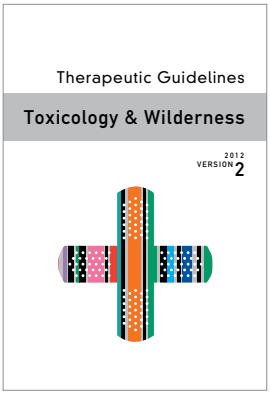
1. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med 1992;327:1637-42.
2. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet 2007;370:657-66.
3. Reid IR, Bolland MJ, Grey A. Effect of calcium supplementation on hip fractures. Osteoporos Int 2008;19:1119-23.
4. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev 2009:CD000227.
5. DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. BMJ 2010;340:b5463.
6. Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet 2005;365:1621-8.
7. Prince RL, Devine A, Dhaliwal SS, Dick IM. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. Arch Intern Med 2006;166:869-75.
8. Reid IR, Mason B, Horne A, Ames R, Reid HE, Bava U, et al. Randomized controlled trial of calcium in healthy older women. Am J Med 2006;119:777-85.
9. Bonnick S, Broy S, Kaiser F, Teutsch C, Rosenberg E, DeLucca P, et al. Treatment with alendronate plus calcium, alendronate alone, or calcium alone for postmenopausal low bone mineral density. Curr Med Res Opin 2007;23:1341-9.
10. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22.
11. McClung M, Miller P, Recknor C, Mesenbrink P, Bucci-Rechtweg C, Benhamou CL. Zoledronic acid for the prevention of bone loss in postmenopausal women with low bone mass: a randomized controlled trial. Obstet Gynecol 2009;114:999-1007.
12. Grey A, Bolland M, Wattie D, Horne A, Gamble G, Reid IR. Prolonged antiresorptive activity of zoledronate: a randomized, controlled trial. J Bone Miner Res 2010;25:2251-5.
13. McCloskey EV, Beneton M, Charlesworth D, Kayan K, deTakats D, Dey A, et al. Clodronate reduces the incidence of fractures in community-dwelling elderly women unselected for osteoporosis: results of a double-blind, placebo-controlled randomized study. J Bone Miner Res 2007;22:135-41.
14. Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. BMJ 2008;336:262-6.

15. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 2010;341:c3691.
16. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al. Calcium/vitamin D supplementation and cardiovascular events. Circulation 2007;115:846-54.
17. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ 2011;342:d2040.
18. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000;342:1478-83.
19. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney Int 2007;71:438-41.
20. Russo D, Miranda I, Ruocco C, Battaglia Y, Buonanno E, Manzi S, et al. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. Kidney Int 2007;72:1255-61.
21. Reid IR, Bolland MJ, Sambrook PN, Grey A. Calcium supplementation: balancing the cardiovascular risks. Maturitas 2011;69:289-95.
22. Sambrook PN, Cameron ID, Chen JS, Cumming RG, Durvasula S, Herrmann M, et al. Does increased sunlight exposure work as a strategy to improve vitamin D status in the elderly: a cluster randomised controlled trial. Osteoporos Int 2011;23:615-24.
23. Reid IR, Bolland MJ, Avenell A, Grey A. Cardiovascular effects of calcium supplementation. Osteoporos Int 2011;22:1649-58.
24. Reid IR, Schooler BA, Hannan SF, Ibbertson HK. The acute biochemical effects of four proprietary calcium preparations. Aust N Z J Med 1986;16:193-7.
25. Rubin MR, Rundek T, McMahon DJ, Lee HS, Sacco RL, Silverberg SJ. Carotid artery plaque thickness is associated with increased serum calcium levels: the Northern Manhattan study. Atherosclerosis 2007;194:426-32.
26. Bolland MJ, Wang TK, van Pelt NC, Horne AM, Mason BH, Ames RW, et al. Abdominal aortic calcification on vertebral morphometry images predicts incident myocardial infarction. J Bone Miner Res 2010;25:505-12.
27. Lind L, Skarfors E, Berglund L, Lithell H, Ljunghall S. Serum calcium: a new, independent, prospective risk factor for myocardial infarction in middle-aged men followed for 18 years. J Clin Epidemiol 1997;50:967-73.
28. Jorde R, Sundsfjord J, Fitzgerald P, Bønaa KH. Serum calcium and cardiovascular risk factors and diseases: the Tromsø study. Hypertension 1999;34:484-90.
29. Foley RN, Collins AJ, Ishani A, Kalra PA. Calcium-phosphate levels and cardiovascular disease in community-dwelling adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J 2008;156:556-63.
30. Leifsson BG, Ahren B. Serum calcium and survival in a large health screening program. J Clin Endocrinol Metab 1996;81:2149-53.
31. Knox EG. Ischaemic-heart-disease mortality and dietary intake of calcium. Lancet 1973;1:1465-7.
32. Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR. Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. Am J Epidemiol 1999;149:151-61.
33. Iso H, Stampfer MJ, Manson JE, Rexrode K, Hennekens CH, Colditz GA, et al. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. Stroke 1999;30:1772-9.
34. Ascherio A, Rimm EB, Hernán MA, Giovannucci EL, Kawachi I, Stampfer MJ, et al. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. Circulation 1998;98:1198-204.
35. Al-Delaimy WK, Rimm E, Willett WC, Stampfer MJ, Hu FB. A prospective study of calcium intake from diet and supplements and risk of ischemic heart disease among men. Am J Clin Nutr 2003;77:814-8.
36. Van der Vijver LP, van der Waal MA, Weterings KG, Dekker JM, Schouten EG, Kok FJ. Calcium intake and 28-year cardiovascular and coronary heart disease mortality in Dutch civil servants. Int J Epidemiol 1992;21:36-9.
37. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Burckhardt P, Li R, Spiegelman D, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. Am J Clin Nutr 2007;86:1780-90.

Book review

Therapeutic Guidelines: Toxicology and Wilderness. Version 2.

Benjamin Close
Emergency physician
The Townsville Hospital
Queensland



Melbourne: Therapeutic Guidelines Limited; 2012. 303 pages

These guidelines aim to present a comprehensive but succinct review based on current evidence and opinion. Topics are arranged by diagnostic entities and include explicit management recommendations.

I found the book well organised. The expert group of authors are well regarded and the guidelines accurately reflect the most up-to-date information available. The use of key point boxes and lists of further readings give the reader the option of how much detail they want to read. However, these features were not present in all sections.

The book has some minor shortcomings. A toxicology topic on local anaesthetics would have been useful as they are widely used particularly in primary care. A discussion on the role of magnesium in Irukandji syndrome is also warranted, despite the controversy over the evidence, as it is still commonly used in certain situations.

This latest edition covers all the key topics in the field in an easily accessible reference format while still providing enough detail to guide specific therapeutic interventions. Clinicians should find it a useful portable guide.