

Calcium supplements: bad for the heart?

Ian R Reid, Mark J Bolland

Calcium is a micronutrient widely believed to affect bone health, though the importance of normal variations in calcium intake may have been over-emphasised.^{1 2} Because its principal dietary source is dairy products, and because high dairy intakes are not acceptable to many older people, there has been a strong move in recent decades to increase the intake of calcium by supplements. This is most prevalent for the prevention of postmenopausal osteoporosis, but is also used in the management of serum phosphate levels in patients with renal failure. However, the safety of calcium supplements is now coming under considerable scrutiny. Their use in osteoporosis had caused concern with respect to the risk of renal calculi, which is increased by about 20%.³ There has also been a longstanding awareness that they cause gastrointestinal symptoms, particularly constipation, but it is more alarming to find that they double the risk of admission to hospital with an acute abdominal condition.⁴ The concern that most threatens their continuing use, however, is their potential risk to cardiovascular health. Although there is trial evidence that calcium supplements can improve high-density lipoprotein/low-density lipoprotein ratios by almost 20%, and reduce both systolic and diastolic blood pressure by a few mm Hg, this does not appear to translate into fewer cardiovascular events. This concern first surfaced in nephrology practice with evidence that calcium supplements exacerbated vascular calcification and contributed to the very high cardiovascular mortality experienced by those patients. Randomised trials in pre-dialysis patients have demonstrated acceleration of coronary artery calcification,⁵ and some trials have shown increased cardiovascular mortality in patients randomised to calcium.⁶

More recently, the focus of concern about cardiovascular safety has moved to osteoporosis management. A trial of 1471 healthy postmenopausal women who were randomised to receive calcium 1 g/day or placebo over 5 years, showed increases of about 40% in cardiovascular event rates in the former group.⁷ Myocardial infarction and stroke were prespecified secondary end points in this trial, and the events were adjudicated. This finding has led to considerably more scrutiny of this area. In a meta-analysis of published cardiovascular events in three clinical trials involving 3861 subjects, Wang *et al* reported a statistically non-significant 14% increase in the risk of a mixture of cardiovascular events with calcium supplements, concluding that these supplements had minimal effects on cardiovascular risk.⁸ This analysis has been superseded by a larger analysis by Bolland *et al* that assessed specific cardiovascular events.⁹ The Bolland analysis systematically collected adverse event data from the 11 major trials of calcium monotherapy (N=11 921), including those assessed by Wang. They found a 31% increase in risk of myocardial infarction, which was statistically significant. The confidence intervals of the Wang and Bolland meta-analyses substantially overlap, so the findings do not contradict one another, but the Wang analysis was clearly underpowered to detect the size of the adverse effect that appears to be present.

Bolland has subsequently studied the cardiovascular effects of calcium supplements combined with vitamin D. The largest trial using this intervention was the Women's Health Initiative, and, again, initial analyses appeared reassuring.¹⁰ However, more than half of the women entering that study were already taking calcium supplements at the time of randomisation, which might have obscured any adverse effects. When analysis was restricted to the 16 000 women who were treatment-naïve at randomisation, the same adverse effect on myocardial infarction emerged with calcium plus vitamin D (HR=1.22), as was found with calcium monotherapy.¹¹

The largest meta-analysis (N=28 072) brings together trials that used either calcium plus vitamin D, or calcium alone as the intervention. It shows remarkable consistency across the major studies, and demonstrates a RR of myocardial infarction of 1.24 (95% CI 1.07 to 1.45) and of stroke of 1.15 (1.00 to 1.32).¹¹

A second series of studies initiated in response to this safety concern has accessed observational databases. In the Kuopio Osteoporosis Study,¹² 10 555 postmenopausal women were followed up for 7 years and the HR for coronary heart disease was 1.24 (95% CI 1.02 to 1.52) in users of calcium supplements.¹² In this issue of *Heart*, Li *et al* have analysed data from the EPIC-Heidelberg cohort and identified no adverse effects associated with dietary calcium intake, but a near doubling of risk of myocardial infarction in calcium supplement users, though the number of calcium supplement users and the numbers of events are surprisingly small.¹³

A problem with all observational studies is that of confounding. In the USA, it is quite clear that women choosing to take calcium supplements have better health profiles at baseline with differences from non-users in age, body mass index, blood pressure, use of hormone replacement therapy, history of myocardial infarction or stroke and smoking.¹¹ This could clearly bias a study towards finding a beneficial effect from calcium supplements even if none existed. In contrast, the Heidelberg study shows fewer baseline differences between calcium users and the rest of the cohort, suggesting a lesser risk of confounding. The consistency of the findings from this and the Kuopio study reinforce the conclusions from the recent meta-analyses of randomised trials.

The meta-analyses have not had the power to determine whether calcium supplement use increases cardiovascular deaths, and that is also the case in the EPIC-Heidelberg cohort, though there are upward trends. Some have used the absence of a proven adverse effect on mortality as a reason not to take the problem seriously. Recent data from a randomised, controlled trial in Australia are sobering. Six hundred and two elderly, frail individuals were randomised to control, daily sunshine exposure, or daily sunshine exposure plus calcium 600 mg/day. Follow-up extended to almost 3 years, during which time there were 218 deaths. Comparisons between the sunshine and sunshine plus calcium groups showed a 47% increase in total mortality (p=0.02)

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and a 76% increase in cardiovascular mortality ($p=0.02$) associated with randomisation to the calcium supplements,^{14 15} very similar to the data from the dialysis literature.

Thus, the evidence is steadily mounting for a real cardiovascular adverse effect from the use of calcium supplements, raising the question as to whether this is large enough to abrogate the beneficial effects on fractures. In fact, the anti-fracture effects of calcium are modest, having been demonstrated in only two studies of calcium plus vitamin D, and suggested to be of the order of about 10% reduction, in meta-analyses.¹⁶ The Bolland meta-analysis of calcium monotherapy demonstrated that the treatment of 1000 older adults with calcium for 5 years resulted in 14 more myocardial infarctions, 10 more strokes and 13 more deaths, to be balanced against 26 fewer fractures.⁹ Similar analyses in younger cohorts also show the net balance to be negative.¹¹ Thus, the consistent evidence is that calcium supplements do more harm than good and that other interventions are preferable for reducing the risk of osteoporotic fractures.

An interesting feature to emerge from the EPIC-Heidelberg cohort is that the adverse effects of calcium supplements on cardiovascular risk are not mirrored in an adverse effect of dietary calcium intake. A parallel situation exists for renal calculi, where supplements increase the risk, but dietary calcium may be protective.¹⁷ How can these differences be explained? There is a substantial observational literature demonstrating that high-normal serum calcium levels are associated with an increased risk of vascular calcification, increased carotid artery atheroma, increased risk of cardiovascular events and increased mortality in comparison with individuals with low-normal serum calcium levels.¹⁸

This suggests that circulating calcium drives the atherogenic process, possibly through calcium sensing receptors on vascular smooth muscle or endothelial cells. Dietary calcium is taken in small amounts spread throughout the day, usually together with fat and protein. As a result, it is absorbed slowly, causing little change in serum calcium levels.¹⁹ In contrast, the large boluses of calcium used as supplements produce substantial increases in serum calcium, frequently raising levels above the normal range.²⁰ Thus, if high-normal serum calcium levels can accelerate

atherogenesis, then supplements might have a similar effect, by producing high-normal serum calcium levels for some hours after each dose. Similar pulses of hypercalciuria are thought to mediate the increase in stone risk with calcium, whereas dietary calcium interferes with absorption of dietary components (eg, oxalate), which themselves contribute to stone formation.

Calcium supplements have been widely embraced by doctors and the public, on the grounds that they are a natural and, therefore, safe way of preventing osteoporotic fractures. It is now becoming clear that taking this micronutrient in one or two daily boluses is not natural, in that it does not reproduce the same metabolic effects as calcium in food. The evidence is also becoming steadily stronger that it is not safe, nor is it particularly effective. Therefore, the bolus administration of this micronutrient should not be encouraged, rather people should be advised to obtain their calcium intake from an appropriately balanced diet. In those at high risk of fracture, interventions of proven anti-fracture efficacy should be used, and these interventions have a fully documented safety profile which is often better than that of calcium. We should return to seeing calcium as an important component of a balanced diet and not as a low-cost panacea to the universal problem of postmenopausal bone loss.

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