Following the publication of an article by Mark Bolland and co-workers\(^1\) in the British Medical Journal of 29 July 2010, on the association between calcium supplementation for osteoporosis and an increased risk of myocardial infarction, much concern and confusion exist among patients and doctors alike as to the safety and efficacy of these agents.

**Is there an association between osteoporosis and cardiovascular disease (CVD)?**

An association between osteoporosis and CVD is well established and numerous studies have demonstrated that CVD and cardiovascular mortality are associated with reduced bone mineral density (BMD) and/or skeletal fractures.\(^2\)\(^-\)\(^4\) These two conditions may be sustained by similar pathophysiological mechanisms (e.g. age-related hypogonadism; proinflammatory cytokines like IL-1, TNF-\(\alpha\); alterations in the RANKL/osteoprotegerin system which is present in both vascular and skeletal tissue) and risk factors (e.g. ageing, smoking, sedentary lifestyle), and may even be amenable to common therapeutic approaches (e.g. bisphosphonates, statins, vitamin D).

Postmenopausal women with osteoporosis have a 3.9-fold higher risk of CVD than women with osteopenia or a normal BMD.\(^5\) Each one standard deviation (SD) decrease in BMD is associated with a 70% increase in stroke risk.\(^6\) The severity of aortic calcification is a good predictor of both hip fracture and myocardial infarction.\(^6\) These associations are well documented in postmenopausal women, but have also recently been demonstrated in men, where a strong correlation between increased bone resorption and CVD was also found.\(^7\) Subjects with osteoporosis may thus benefit from screening for cardiovascular disease. Moreover, treatment of osteoporosis with potent bisphosphonates like zoledronic acid has been shown to reduce overall mortality by 25–30%. A decrease in fracture incidence accounted for less than 10% of the reduction in overall mortality, which largely resulted from a reduction in CVD.\(^8\)

**What was known about the efficacy and safety of calcium supplementation in osteoporosis prior to the Bolland article?**

The effects of calcium with or without vitamin D supplementation on peak bone mass attainment, age-related bone loss and fracture risk remain uncertain. The influence of calcium supplementation on the largely genetically determined peak bone mass is modest at best, and appears to vary depending on the dose, baseline calcium intake, skeletal sites examined, pubertal maturation and genetic factors.\(^9\)\(^-\)\(^12\) Calcium deficiency has a more pronounced effect on age-related bone loss, and intervention later in life appears to be more beneficial, but again the data are not robust.\(^13\)\(^-\)\(^17\) What about the role of calcium in reducing the risk of fracture? Earlier studies showed that calcium and vitamin D supplementation significantly reduced the risk of fracture, and meta-analyses in 1997\(^18\) and in 2005\(^19\) suggested that supplementation with 1 g of calcium plus vitamin D 800 IU per day, was associated with a 20–25% reduction in hip fracture. A number of recent publications have, however, challenged the anti-fracture efficacy of calcium and vitamin D.\(^20\)\(^-\)\(^22\) Although many of these studies did not target individuals at high fracture risk, often employed an inadequate dose of vitamin D (≤ 400 IU per day) and/or did not take cognisance of the poor compliance with calcium supplementation, the role of calcium in fracture prevention would appear to be modest. Calcium has, however, been a mandatory component of every drug trial using potent antifracture medicines (e.g. the bisphosphonates or strontium ranelate) and is thought to have an additive effect when used in combination with these drugs.\(^23\)\(^,\)\(^24\) These studies employing...
antifracture drugs plus calcium have generally been associated with a significant reduction in all-cause mortality, not infrequently with a significant reduction in cardiovascular mortality.3

Although the antifracture efficacy of calcium may be uncertain, calcium supplementation has generally been regarded as safe. An adequate dietary calcium intake is associated with a significantly lower incidence of CVD and stroke.26–27 Calcium supplements have been shown to reduce risk factors for CVD like hypertension and dyslipidaemia.28–30 To date, calcium supplementation has been regarded as safe, although it is known to increase arterial calcification and mortality in subjects with renal failure.31,32 The large Women’s Health Initiative (WHI) (27 000 subjects) showed that individuals taking calcium and a low dose Vitamin D supplement tended to have a lower mortality,33 and no adverse effects on cardiovascular health.34

The Bolland articles

In 2008, Bolland and co-workers published the results of their randomised controlled trial (RCT) on vascular events in healthy elderly women receiving calcium supplements, which showed a non-significant trend towards a higher incidence of CVD in those subjects receiving calcium.35 This was followed up in 2010 by a meta-analysis of 15 RCTs involving some 12 000 subjects taking calcium supplements for osteoporosis.1 Of note is the fact that trials involving additional vitamin D supplementation were excluded from the study. Compared with placebo, patients taking calcium supplements had a modest (27%), but significant increase in myocardial infarction. None of the individual RCTs from which this meta-analysis was compiled, reported any significant cardiovascular effects. No significant increase in mortality or incidence of stroke was reported in this study.

The current study selected RCTs with an exceptionally high dose of supplemental calcium, the average dose being 1 200 mg/day, with some studies employing 1 500–2 000 mg/day. Furthermore, the dietary calcium intake in these subjects was above average (900 mg/day) and a positive correlation was found between the proposed increase in cardiovascular disease (CVD) and the dietary intake of calcium. In fact, the increase in CVD was entirely limited to those with a dietary calcium intake of more than 800 mg/day – no increased risk being found in subjects with a dietary calcium intake below 800 mg/day.

National Osteoporosis Foundation of South Africa (NOFSA) recommendations

The Bolland meta-analysis clearly differs from previous epidemiologic studies which documented a 30–40% lower risk of CVD and ischaemic stroke in subjects in the top quartile of calcium intake.26–27 Whether this reflects a fundamental difference in the source (dietary vs. supplements) or total dose of calcium remains unclear. The Bolland paper also differs from previous intervention studies, including the WHI, which showed that individuals taking calcium and a low dose Vitamin D supplement tended to have a lower mortality,33 and no adverse effects on cardiovascular health.34 Again it is unclear whether this is a function of the supplemental vitamin D which was included in studies like the WHI and specifically excluded in the Bolland meta-analysis.

Clearly more information is necessary before robust evidence-based recommendations can be made. In the interim, NOFSA would recommend the following:

• An adequate calcium intake is important for normal bone health. This should preferably be accomplished by consuming sufficient dairy (low fat) products in the diet.
• Calcium supplementation is, however, often required and in a dose of 500 mg/day is acceptable and safe.
• Such calcium supplementation, especially when it accompanies vitamin D and/or one of the potent bone-active drugs for the management of osteoporosis, should be continued since there is no evidence that it increases the risk of CVD.
• High-dose calcium supplementation in patients already consuming ample dairy, and especially in those with known kidney failure or CVD, is unnecessary and should be avoided.

References


