Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Review article: Current opinion | Published 31 August 2011, doi:10.4414/smw.2011.13260
Cite this as: Swiss Med Wkly. 2011;141:w13260

Calcium supplementation, osteoporosis and cardiovascular disease

Christian Meier, Marius E. Kraenzlin

Division of Endocrinology, Diabetes and Metabolism, University Hospital, Basel, Switzerland

Summary

Adequate intakes of calcium and vitamin D are essential preventive strategies and essential parts of any therapeutic regimen for osteoporosis. However, calcium supplementation is not without controversy and benefits on skeletal health need to be balanced against potential risks on cardiovascular disease. The published data so far suggest a potential detrimental effect of calcium supplement on cardiovascular health (i.e. myocardial infarction) although further prospective studies are needed to clarify the gradient of risk. Since food sources of calcium produce similar benefits on bone density as supplements and dietary calcium intake does not seem to be related with adverse cardiovascular effects, calcium intake from nutritional sources needs to be enforced. In patients with low calcium intake supplements are warranted aiming for a total calcium intake of 800 to 1000 mg/d together with adequate vitamin D replacement. Nevertheless we should keep in mind that for significant reduction in fracture risk, pharmacological treatment is mandatory in patients at risk of fractures irrespective of calcium and vitamin D supplementation.

Key words: *calcium; osteoporosis; fracture; cardiovascular disease; coronary heart disease*

Introduction

Osteoporosis is a worldwide health issue. It is anticipated that the number of affected individuals, and thereby costs to health care systems, will increase substantially with further aging of the population. Of all the preventive strategies for age-related bone loss and osteoporotic fractures adequate calcium intake is the simplest and least expensive. However, calcium supplementation is not without controversy. In contrast to its effect in maintaining bone mineral density (BMD) in adults its anti-fracture efficacy remains unsettled. Furthermore, controversy has been fuelled after the publication of studies suggesting a potential negative effect of calcium supplementation on cardiovascular health. Specifically, a recent meta-analysis on the effect of calcium supplements on the risk of myocardial infarction and cardiovascular events has questioned the need for and the safety of daily calcium supplementation [1] . Not only patients but also health care providers are left with uncertainties about the risks and benefits of calcium supplementation. In this review we will briefly summarize the effects of calcium supplementation on the skeletal and cardiovascular system and conclude with practical recommendations for the care of patients at risk for osteoporotic fractures. As several articles recently reviewed the influence of vitamin D on skeletal and non-skeletal endpoints, we will focus largely on the potential benefits and risks of calcium supplementation.

Calcium supplementation and skeletal health

Effects of calcium supplementation on bone loss

Inadequate intake of calcium and vitamin D results in reduced calcium absorption with secondary hyperparathyroidism and consecutive bone loss. As bone loss is a strong predictor of fracture calcium supplementation combined with vitamin D has become one of the most widely accepted strategies in primary and secondary prevention of osteoporosis.

Several studies have shown the effectiveness of calcium supplementation in slowing or stopping bone loss [2–5] . In a meta-analysis by Shea et al. the effect of calcium on bone density has been confirmed in postmenopausal women. In this study including 15 trials (1806 patients) the authors found calcium to be more effective than placebo in reducing rates of bone loss after two or more years of treatment, specifically for secondary prevention [6]. Notably, the mean total calcium intake in the calcium trials was mostly above 1000 mg/day (with a dietary calcium intake of 408 to 879 mg/d and additional calcium supplementation between 500 and 2000 mg/d). A recent meta-analysis extended these findings in a larger cohort including 29 randomized trials (63897 patients) reporting that calcium supplementation, alone or in combination with vitamin D, is effective in reducing bone loss at the hip and the spine in women and men aged 50 years or older [7] .

After reaching peak bone mass there is an age-related yearly bone loss in both sexes of about 1% [8], which is accelerated to 2% for up to 14 years in women around the age of menopause [9]. To keep bone loss to a minimum, increased dietary calcium is needed, or calcium supplementation needs to be added in order to maintain a total daily calcium intake of about 1000 mg.

Effects of calcium supplementation on fracture risk

In contrast to the effectiveness of calcium supplementation in slowing bone loss, its influence on fracture risk is still a matter of debate. The controversy is in part attributable to the relatively small number of studies that have addressed fracture endpoints. More importantly, the available trials are heterogeneous with respect to the dose and preparation of calcium used, whether calcium is used as monotherapy or in combination with vitamin D, whether patients were adherent to the supplementation regimen, and lastly due to differences in study populations (e.g. age, gender, magnitude of fracture risk, institutionalised versus community-dwelling) [10]. According to various studies which used a combined intervention of calcium and vitamin D, fracture risk was reduced in frail elderly populations [11–13] . In their meta-analysis including 29 randomized trials, Tang et al. reported that calcium supplementation (alone or in combination with vitamin D) is effective in preventing osteoporotic fracture in elderly women and men. The risk of any fracture was reduced over average treatment duration of 3.5 years (RR 0.88, 95%CI 0.83–0.95). Interestingly, the fracture risk reduction was greatest in individuals who were elderly, lived in institutions, had a low body weight, had a low calcium intake or were at high baseline fracture risk. For calcium-only supplementation, a minimum dose of 1200 mg was needed for favourable treatment effect [7] . In a randomized placebo-controlled trial among healthy community-dwelling older men and women, Bischoff-Ferrari et al. showed that four years of supplementation with 1200 mg calcium alone is associated with a reduction in risk of all fractures and minimal trauma fractures. After supplementation was stopped the benefit of calcium was lost [14] .

Two concerns need further attention. Firstly, as with other medical interventions that need long-term adherence, compliance has been shown to be poor in some studies limiting the beneficial effect of calcium supplementation on fracture risk. A number of studies [15–17] show no significant benefit when data were analysed using an intention-to-treat approach, but trends toward benefit in per-protocol analyses [10]. Secondly, reduction in total fracture risk does not necessarily imply that risk for specific fracture types, such as hip fractures are also reduced. Reid et al. reanalysed the Tang meta-analysis considering only hip fractures and found a non-significant relative risk reduction associated with calcium use 0.91 (95%CI 0.80–1.04). Subgroup analyses showed that the relative risk of hip fracture was significantly lower for combined supplementation (calcium plus vitamin D; RR 0.84, 95%CI 0.73–0.97) than that for calcium supplementation alone (RR 1.50, 95%CI 1.06–2.12). Furthermore and in accordance with two other trials [16, 18] , calcium supplementation alone was associated with an increased risk of hip fracture. Meta-analysis of these three studies demonstrates a relative risk of hip fracture of 1.50 (95%CI 1.06–2.12) on calcium supplementation alone [10]. In contrast and according to a recent meta-analysis, nutritional calcium intake (such as milk consumption) was not associated with hip fracture risk in women and men [19].

These findings suggest that calcium supplementation alone without adequate vitamin D intake is not an appropriate preventive strategy to reduce hip fracture risk. The study by Boonen et al. confirmed that only in combination with vitamin D may calcium intake reduce the risk of hip and any non-vertebral fractures [20].

Calcium supplementation and cardiovascular disease

Based on interventional studies it has generally been proposed that calcium supplements may have favourable effects on the cardiovascular system by its effects on intestinal fat absorption and blood pressure. It was suggested that calcium supplements are binding lipids and bile acids in the gut thereby interfering with fat absorption [21–22] . A recent meta-analysis of randomized, controlled trials investigating faecal fat excretion in relation to calcium intake (supplements or dairy) confirmed increased fat excretion to an extent that could be relevant for prevention of weight gain [23] . Indeed, observational studies have found that dietary calcium intake is inversely related to body weight and body fat mass [24]. In contrast, however, other studies questioned a beneficial effect of calcium on lipid metabolism. A recent study by Reid et al. found no significant treatment effect of calcium intake on the ratio of HDL to LDL cholesterol nor on weight, fat mass, lean mass, triglycerides, or total, LDL, or HDL cholesterol [25] .

More consistent are data on the effect of calcium treatment on blood pressure with demonstration of average decrements of 1 to 2 mm Hg in both systolic and diastolic pressures [26–28] . In the most recent randomized controlled trial there were downward trends in systolic and diastolic blood pressures within the calcium-supplemented groups, but there were no significant treatment effects over the whole trial period of two years [25] . In a post hoc analysis of those with baseline calcium intake below the median value (<785 mg/d), blood pressures showed borderline treatment effects as compared with placebo; hence calcium supplementation may decrease blood pressure in those with low dietary intakes. The effects of calcium supplementation on blood pressure are probably induced by the natriuretic effect of calcium [29].

Potential negative cardiovascular effects of calcium supplements

Whether these modest changes in cardiovascular risk factors ultimately result in improved cardiovascular morbidity and mortality is questioned since recent studies have suggested that calcium supplementation may be harmful and associated with increased vascular events.

In a five year randomized, placebo-controlled trial in 1471 healthy older women (mean age 74 years) Bolland et al. reported increases in rates of cardiovascular events in women allocated to calcium supplements (calcium citrate, 1000 mg). Contrary to the study's hypothesis of benefit, subjects' self-reports of adverse events showed a two-fold excess of myocardial infarction (RR 2.12, 95%CI 1.01–4.47) and a non-significant increase in the risk of stroke (RR 1.37, 95%CI 0.83–2.28) [30] . Based on this meta-analysis and its absolute risk estimates a NNH for myocardial infarction of 210 and a NNH for stroke of 476 over five years can be calculated (table 1).

Subsequently the same authors performed a meta-analysis of cardiovascular events in randomized, placebo-controlled studies of calcium supplements (without vitamin D co-administration). Most patients included in the analysis were women (median age of 74.5 years) and their mean dietary calcium at baseline ranged between 400 and 1200 mg/d. It remains unclear to what extent cardiovascular risk factors (e.g. hypertension, diabetes or lipid disorders) were prevalent as these data were not available in most studies included into the meta-analysis. Calcium supplements (calcium citrate or gluconate, 500–2000 mg) significantly increased the risk of myocardial infarction by 31% in five trials involving 8151 participants where individual patient data were available, and by 27% in 11 trials involving 11921 participants where trial level data were available. There were no statistically significant increases in the risk of stroke or death [1] .

Both studies have received major attention due to the potential detrimental effect on cardiovascular health, nevertheless major criticism has also been raised [29, 31] . In the first trial the risk of myocardial infarction was no longer significantly increased once the data had undergone a quality control audit using the national database of hospital admissions. The meta-analysis showed a significant increase in myocardial infarction, although none of the studies by itself observed significant results, not even the largest one. Importantly, data on cardiovascular events were collected from self-reports, death certificates and medical records, but were not defined as primary study endpoints. These and other criticisms, such as the fact that no attenuation of mortality has been observed, have been carefully addressed by the authors concluding that calcium supplementation should be used with caution in particular as potential benefits on skeletal health seem limited [29].

In contrast to the findings of Bolland et al., a recently published interventional trial of calcium carbonate showed no negative cardiovascular effect. This study examined atherosclerotic vascular hospitalisation and mortality data from a 5-year randomized controlled trial with a 4.5 year post-trial follow-up [32]. The participants were 1460 women (mean age 75 years) recruited from the general population and randomized to receive 1200 mg calcium carbonate daily or placebo. The intervention group that received calcium supplementation did not have a higher risk of death or first-time hospitalisation from atherosclerotic vascular disease in either the 5-year RCT or during the 9.5 years of observational study. Of note, the results of this study are not directly comparable with the meta-analysis by Bolland et al. [1] as they choose a broad composite endpoint of atherosclerotic vascular disease (including atrial fibrillation and congestive heart failure) without analysis of specific endpoints such as myocardial infarction or stroke.

Whereas these studies examined the effect of calcium monotherapy the question arises whether co-administered calcium and vitamin D affects cardiovascular risk or whether the potential negative effect of calcium on cardiovascular events might be attenuated in combined treatment. There is some evidence that vitamin D might have an independent beneficial effect on mortality [33–35] . In a randomized, placebo-controlled trial over seven years the Women's Health Initiative reported no adverse effect of calcium and vitamin D (1000 mg calcium and 400 IU vitamin D daily) on any cardiovascular endpoint [36] . Importantly, 54% of the participants were taking personal (non-protocol) calcium supplements at randomization (total calcium intake, exclusive study medication: app. 1150 mg/d) and 47% were taking personal vitamin D supplements (total vitamin D intake, exclusive study medication: app. 365 IU/d). This study has been reanalysed taking into account the interaction of personal use of calcium supplements [37]. The authors conclude that calcium supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially myocardial infarction (HR 1.22, 95%CI 1.00–1.50), a finding obscured in the WHI calcium/vitamin D study by the widespread use of personal calcium supplements. The risk for myocardial infarction and stroke (HR 1.17, 95%CI 0.95–1.44) were similar to those observed in the meta-analysis by Bolland et al. [1] . In women taking personal calcium supplements at randomization, the addition of calcium and vitamin D did not increase cardiovascular risk suggesting that there may not be a dose-response relationship between calcium supplement and the risk of cardiovascular events [37]. The concept that abrupt change in plasma calcium concentration (which results after supplement ingestion) may be responsible for the observed increased cardiovascular risk remains speculative.

A meta-analysis by Wang et al. including four prospective studies of healthy persons found no differences in incidence of cardiovascular disease between calcium supplement recipients and non-recipients. Results of secondary analyses in eight randomized trials showed a slight but statistically non-significant risk reduction in cardiovascular disease with vitamin D supplementation at moderate to high doses (app. 1000 IU/d) but not with calcium supplementation, or a combination of vitamin D and calcium supplementation [38].

To judge whether the observed effect of calcium supplements on cardiovascular endpoints represents a reliable signal which needs further attention one would like to understand possible mechanisms relating calcium supplementation with vascular disease. Although speculative some

Table 1: Benefits and risks of calcium supplementation. Treatment effect estimation (NNT/NNH) based on data from published meta-analyses evaluating the effect of calcium supplements on fracture risk and cardiovascular events (treatment duration 4–5 years) [1, 10, 63].

	Calcium group, number events	**Control group, number events**	**NNT / NNH**
Benefit?			
Non-vertebral fracture	388/3356>	426/3384	NNT 74
Hip fracture	77/2773	52/2801	NNT 109
Harm?			
Myocardial infarction	>166/6116	130/5805	NNH 210
Stroke	212/6116	190/5805	NNH 476

interesting mechanisms have been discussed in a recent review by Reid et al. [29].

Several studies have shown transient increases in serum calcium levels into the borderline hypercalcaemic range following ingestion of 500 to 1000 mg calcium as a supplement [39–40] which is in contrast to the intake of calcium from dietary sources. Ingestion of calcium-rich foods has been shown to result in much smaller changes in circulating calcium levels, which might be due to slower intestinal transit as calcium rich foods are usually ingested together with proteins and fat [41] . A systematic review recently showed that dairy food consumption is not associated with a higher risk of coronary heart disease [42].

In contrast, however, high-normal levels of serum calcium have been related to cardiovascular disease, including carotid artery plaque thickness [43] and abdominal aortic calcification [44] . Direct correlations between serum calcium levels and coronary heart disease [45–47] or stroke [45, 48] have been observed in postmenopausal women and men as well as in patients with primary hyperparathyroidism [49]. Hence, one could assume that calcium supplements, not taken together with meals, would result in elevations of circulating calcium above the upper normal range. In fact, hypercalcaemia after intake of calcium supplements is transitory lasting for about six hours [29]. Repeated intake of supplements with repeated calcium peaks may therefore translate into increased risk of cardiovascular disease.

Other potential mechanisms linking calcium supplements with cardiovascular disease include acceleration of coronary artery calcification [50–51] , induction of a hypercoagulable state [52–53] and effects on arterial stiffness with impaired vasodilatation [54–56] .

Practical consequences

A general function of everyday clinical practice is the identification of persons with an increased risk of fractures, the initiation of preventive measures and the institution of a therapeutic intervention appropriate to their individual fracture risk. Nowadays, a case-finding strategy that is designed to investigate people (by DXA) with a clearly increased risk of fracture is recommended [57] . Drug therapy is indicated where there is increased risk of fracture. This applies to patients who have already experienced a fracture, especially a vertebral or hip fracture or patients with an increased absolute 10-year fracture risk (assessed by the "WHO Fracture Risk Assessment Tool" (FRAX©) [58–59]).

Antiresorptive preparations, particularly bisphosphonates, denosumab and selective oestrogen receptor modulators are primarily used in the therapy of osteoporosis. In this context it is noteworthy that calcium supplementation is only a weak resorption inhibitor which is reflected by the small effect on fracture risk reduction [7] . Hence, while adequate calcium intake should generally be ensured as a preventive strategy additional pharmacological treatment is mandatory in patients with increased fracture risk and treatment to prevent fractures cannot exclusively be based on calcium and vitamin D supplementation (except for the rare case of osteomalacia).

The recently published report of the Institute of Medicine in the USA (IOM) states that 1000–1200 mg of calcium is the estimated average daily requirement for women and men over 50 years with a upper limit (that is likely to pose no risk) of 2000 mg/d [60]. As comprehensively discussed in an editorial by Burckhardt [31] these figures are derived from studies in populations whose bone health was not optimal. Importantly, these studies were not titrated against circulating levels of 25(OH)vitamin D which is crucial considering the role of vitamin D in the regulation of intestinal calcium absorption. It therefore seems reasonable to assume that the recommendations of the IOM may be too high.

In clinical practice assessment of an individual's dietary calcium intake is recommended before prescribing additional calcium supplements and calcium supplementation should be restricted to patients with low calcium intake only (<800 mg/d). Dietary calcium intake can be assessed by simplified questionnaires. It has to be acknowledged, however, that this is only a simplified estimate of calcium intake, more precise assessment with thorough quantification should be based on questionnaires such as the Food Frequency Questionnaire (FFQ). Using a semiquantitative questionnaire in daily routine we observed that most patients in our Osteoporosis Clinic generally have sufficient nutritional calcium intake. In a review of 1461 consecutive patients who were referred for osteoporosis assessment a median dietary calcium intake of 1020 mg/d (range, 100–3600 mg/d) was recorded. 73% of patients reported having a daily calcium intake of more than 800 mg. This indicates that routine supplementation of calcium is not warranted in all patients, but patients with inadequate intake need to be identified and treated aiming for a total daily calcium intake of 800 to 1000 mg.

In a posthoc analysis of the meta-analysis by Bolland et al. suggesting an overall increased cardiovascular risk in patients on calcium supplementation [1, 29] there was an interaction between dietary calcium intake and the risk of myocardial infarction. When the cohort was divided into two groups by baseline dietary calcium intake (above and below the median) there was an interaction between dietary calcium and the risk of myocardial infarction with increased risk in patients with a daily intake above 800 mg. In contrast, risk of myocardial infarction was not elevated in women with an intake below 800 mg ($p = 0.01$ for interaction).

As the risk of cardiovascular events is predominantly observed in studies with higher doses of calcium supplements (1000–2000 mg), lower doses seem to be safe. Practically, this indicates that a total calcium intake of about 800 mg (dietary calcium intake and calcium supplement) would be adequate, as long as optimal vitamin D levels are ascertained.

In contrast to the ingestion of calcium-rich foods, calcium supplements taken in the fasting state may result in transient hypercalcaemia (which has been related to cardiovascular disease). In order to prevent relevant hypercalcaemia supplements should be taken after meals and higher doses of supplements are preferably divided into portions of 500 mg.

In summary, potential negative effects of calcium supplements need to be balanced against the benefits of treatment. The published data so far suggest a potential detrimental

effect of calcium supplement on cardiovascular health (i.e. myocardial infarction) although further prospective studies are needed to clarify the gradient of risk. Since food sources of calcium produce similar benefits on bone density as supplements [61–62] and dietary calcium intake does not seem to be related to adverse cardiovascular effects, calcium intake from nutritional sources needs to be enforced. In patients with low calcium intake supplements are warranted aiming for a total calcium intake of 800 to 1000 mg/d together with adequate vitamin D replacement. Nevertheless we should keep in mind that for a significant reduction in fracture risk, pharmacological treatment is mandatory in patients at risk of fractures irrespective of calcium and vitamin D supplementation.

Funding / potential competing interests: No financial support and no other potential conflict of interest relevant to this article were reported.

Correspondence: *Christian Meier, MD, Division of Endocrinology, Diabetes and Metabolism, University Hospital Basel, Missionsstrasse 24, CH-4055 Basel, christian.meier@unibas.ch*

References

1 Bolland MJ, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010;341:c3691.

2 Prince RL, et al. Prevention of postmenopausal osteoporosis. A comparative study of exercise, calcium supplementation, and hormone-replacement therapy. N Engl J Med. 1991;325(17):1189–95.

3 Dawson-Hughes B, et al. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. N Engl J Med. 1990;323(13):878–83.

4 Smith EL, et al. Calcium supplementation and bone loss in middle-aged women. Am J Clin Nutr. 1989;50(4):833–42.

5 Prince R, et al. The effects of calcium supplementation (milk powder or tablets) and exercise on bone density in postmenopausal women. J Bone Miner Res. 1995;10(7):1068–75.

6 Shea B, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. Endocr Rev. 2002;23(4):552–9.

7 Tang BM, et al. 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(9588):657–66.

8 Jones G, et al. Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo osteoporosis epidemiology study. BMJ. 1994;309(6956):691–5.

9 Ahlborg HG, et al. Bone loss and bone size after menopause. N Engl J Med. 2003;349(4):327–34.

10 Reid IR, Bolland MJ, Grey A. Effect of calcium supplementation on hip fractures. Osteoporos Int. 2008;19(8):1119–23.

11 Dawson-Hughes B, et al. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997;337(10):670–6.

12 Chapuy MC, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med. 1992;327(23):1637–42.

13 Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: A pragmatic population-based 3-year intervention study. J Bone Miner Res. 2004;19(3):370–8.

14 Bischoff-Ferrari HA, et al. Effect of calcium supplementation on fracture risk: a double-blind randomized controlled trial. Am J Clin Nutr. 2008;87(6):1945–51.

15 Reid IR, et al. Randomized controlled trial of calcium in healthy older women. Am J Med. 2006;119(9):777–85.

16 Prince RL, et al. 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(8):869–75.

17 Jackson RD, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354(7):669–83.

18 Grant AM, 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(9471):1621–8.

19 Bischoff-Ferrari HA, et al. Milk intake and risk of hip fracture in men and women: a meta-analysis of prospective cohort studies. J Bone Miner Res. 2011;26(4):833–9.

20 Boonen S, et al. Need for additional calcium to reduce the risk of hip fracture with vitamin d supplementation: evidence from a comparative metaanalysis of randomized controlled trials. J Clin Endocrinol Metab. 2007;92(4):1415–23.

21 Yacowitz H, Fleischman AI, Bierenbaum ML. Effects of Oral Calcium Upon Serum Lipids in Man. Br Med J. 1965;1(5446):1352–4.

22 Govers MJ, Van der Meet R. Effects of dietary calcium and phosphate on the intestinal interactions between calcium, phosphate, fatty acids, and bile acids. Gut. 1993;34(3):365–70.

23 Christensen R, et al. Effect of calcium from dairy and dietary supplements on faecal fat excretion: a meta-analysis of randomized controlled trials. Obes Rev. 2009;10(4):475–86.

24 Lanou AJ, Barnard ND. Dairy and weight loss hypothesis: an evaluation of the clinical trials. Nutr Rev. 2008;66(5):272–9.

25 Reid IR, et al. Effects of calcium supplementation on lipids, blood pressure, and body composition in healthy older men: a randomized controlled trial. Am J Clin Nutr. 2010;91(1):131–9.

26 Griffith LE, et al. The influence of dietary and nondietary calcium supplementation on blood pressure: an updated metaanalysis of randomized controlled trials. Am J Hypertens. 1999;12(1 Pt 1):84–92.

27 Reid IR, et al. Effects of calcium supplementation on body weight and blood pressure in normal older women: a randomized controlled trial. J Clin Endocrinol Metab. 2005;90(7):3824–9.

28 van Mierlo LA, et al. Blood pressure response to calcium supplementation: a meta-analysis of randomized controlled trials. J Hum Hypertens. 2006;20(8):571–80.

29 Reid IR, et al. Cardiovascular effects of calcium supplementation. Osteoporos Int. 2011.

30 Bolland MJ, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. BMJ. 2008;336(7638):262–6.

31 Burckhardt P. Potential negative cardiovascular effects of calcium supplements. Osteoporos Int. 2011.

32 Lewis JR, et al. Calcium supplementation and the risks of atherosclerotic vascular disease in older women: results of a 5-year RCT and a 4.5-year follow-up. J Bone Miner Res. 2011;26(1):35–41.

33 Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med. 2007;167(16):1730–7.

34 Melamed ML, et al. 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med. 2008;168(15):1629–37.

35 Anderson JL, et al. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. Am J Cardiol. 2010;106(7):963–8.

36 Hsia J, et al. Calcium/vitamin D supplementation and cardiovascular events. Circulation. 2007;115(7):846–54.

37 Bolland MJ, et al. 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.

38 Wang L, et al. Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events. Ann Intern Med. 2010;152(5):315–23.

39 Karp HJ, Ketola ME, Lamberg-Allardt CJ. Acute effects of calcium carbonate, calcium citrate and potassium citrate on markers of calcium and bone metabolism in young women. Br J Nutr. 2009;102(9):1341–7.

40 Heller HJ, et al. Pharmacokinetic and pharmacodynamic comparison of two calcium supplements in postmenopausal women. J Clin Pharmacol. 2000;40(11):1237–44.

41 Green JH, Booth C, Bunning R. Acute effect of high-calcium milk with or without additional magnesium, or calcium phosphate on parathyroid hormone and biochemical markers of bone resorption. Eur J Clin Nutr. 2003;57(1):61–8.

42 Gibson RA, et al. The effect of dairy foods on CHD: a systematic review of prospective cohort studies. Br J Nutr. 2009;102(9):1267–75.

43 Rubin MR, et al. Carotid artery plaque thickness is associated with increased serum calcium levels: the Northern Manhattan study. Atherosclerosis. 2007;194(2):426–32.

44 Bolland MJ, et al. Abdominal aortic calcification on vertebral morphometry images predicts incident myocardial infarction. J Bone Miner Res. 2010;25(3):505–12.

45 Slinin Y, et al. Serum calcium, phosphorus and cardiovascular events in post-menopausal women. Int J Cardiol. 2010.

46 Lind L, et al. Serum calcium: a new, independent, prospective risk factor for myocardial infarction in middle-aged men followed for 18 years. J Clin Epidemiol. 1997;50(8):967–73.

47 Jorde R, et al. Serum calcium and cardiovascular risk factors and diseases: the Tromso study. Hypertension. 1999;34(3):484–90.

48 Foley RN, et al. Calcium-phosphate levels and cardiovascular disease in community-dwelling adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J. 2008;156(3):556–63.

49 Walker MD, Silverberg SJ. Cardiovascular aspects of primary hyperparathyroidism. J Endocrinol Invest. 2008;31(10):925–31.

50 Russo D, et al. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. Kidney Int. 2007;72(10):1255–61.

51 West SL, Swan VJ, Jamal SA. Effects of calcium on cardiovascular events in patients with kidney disease and in a healthy population. Clin J Am Soc Nephrol. 2010;5(Suppl 1):S41–7.

52 Hilgard P. Experimental hypercalcaemia and whole blood clotting. J Clin Pathol. 1973;26(8):616–9.

53 James MF, Roche AM. Dose-response relationship between plasma ionized calcium concentration and thrombelastography. J Cardiothorac Vasc Anesth. 2004;18(5):581–6.

54 Neunteufl T, et al. Impairment of endothelium-independent vasodilation in patients with hypercalcemia. Cardiovasc Res. 1998;40(2):396–401.

55 Baykan M, et al. Impairment of flow mediated vasodilatation of brachial artery in patients with primary hyperparathyroidism. Int J Cardiovasc Imaging. 2007;23(3):323–8.

56 Nilsson IL, et al. Endothelial vasodilatory function and blood pressure response to local and systemic hypercalcemia. Surgery. 2001;130(6):986–90.

57 Kanis JA, et al. Case finding for the management of osteoporosis with FRAX – assessment and intervention thresholds for the UK. Osteoporos Int. 2008;19(10):1395–408.

58 Kanis JA, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2008;19(4):399–428.

59 Kraenzlin ME, Meier C. Schlaglichter 2010: Neue Wege in der Diagnostik und Therapie der Osteoporose. Swiss Med Forum. 2011;11(3):25–8.

60 Ross AC, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011;96(1):53–8.

61 Lau EM, et al. Milk supplementation of the diet of postmenopausal Chinese women on a low calcium intake retards bone loss. J Bone Miner Res. 2001;16(9):1704–9.

62 Cadogan J, et al. Milk intake and bone mineral acquisition in adolescent girls: randomised, controlled intervention trial. BMJ. 1997;315(7118):1255–60.

63 Bischoff-Ferrari HA, 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(6):1780–90.