

Calcium supplementation and risk of cardiovascular disease

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Summary

With the outcome to demonstrate the efficacy of calcium to prevent the incidence of fractures many randomized controlled trials have been performed in the past two decades, with conflicting results. A RR of 0.86 for non-vertebral fractures and a RR of 0.91 for hip fractures on eight trials were demonstrated. Calcium supplementation is considered particularly important when baseline calcium intake is low. More recently WHI CaD Study indicated that calcium supplements with or without vitamin D represent a factor risk for cardiovascular events. On the other hand the beneficial effect of a correct calcium intake in attaining and maintaining bone mass across the life is largely demonstrated. There is an urgent need for more research to gain insight into the mechanisms of the adverse vascular effect of calcium. Moreover, more extensive data about the incidence of cardiovascular adverse events coming from randomized controlled intervention trials in osteoporosis, in which calcium plus Vitamin D were utilized, might be achieved.

KEY WORDS: calcium; vitamin D; osteoporosis; fracture; prevention.

Introduction

Calcium plays a fundamental role in promoting bone health, as well as in blood coagulation, muscle contraction and regulation of nerve excitability. 1200 mg/day of calcium for men and women aged over 50 years has been proposed by the US National Academy of Sciences as an adequate intake, whereas 1000 mg/day is considered sufficient for younger adults (1). European guideline recommend lower dosages, 800 mg/day for women aged 50-65 years. In the elderly, both those living in the community as well as institutions, the dietary calcium intake is commonly low. In a cohort of elderly community-dwelling French women calcium intake was calculated to be 569 mg/day (2). Our experience confirms these data, underlining that mean calcium intake in elderly people may be sometime less than 600 mg/day (3). New estimates from NHANES shows that American adults are characterized by an age-related decline in calcium intake, partly explained by a concurrent decline in energy intake, while sup-

plemental calcium use are highest in older age groups (4). Moreover patients with documented osteoporosis generally also have an inadequate dietary calcium intake. A review of baseline data from six of the major osteoporosis trials revealed that 85% of participants had calcium intakes <1200 mg at study entry, with a mean of 727 mg/day (5). Nevertheless, definition of the optimal calcium intake is hampered by several uncertainties. It was suggested that a calcium intake >800 mg/day is not necessary for preventing an increase of serum PTH when serum 25(OH)D > 25 nmol/l (6). A meta-analysis of prospective cohort studies and clinical trials did not show a decreased fracture risk with a high vs. low calcium intake (7). In the Women's Health Initiative, a trial in 36,282 women with calcium 1000 mg/day and vitamin D 400 IU/day vs. double placebo, the incidence of kidney stones increased with 17%. Low intakes may cause secondary hyperparathyroidism, while high intakes carry a risk of side effects. A total intake from diet and supplements of about 1000 mg/d probably is sufficient and safe.

Usually calcium supplementation is associated with vitamin D. Vitamin D is essential for maintaining calcium homeostasis. 10, mainly regulating intestinal calcium absorption. Circulating 25(OH)D levels indicative of a deficiency state is typically defined as <25 nmol/l. In the presence of inadequate vitamin D status, calcium absorption is reduced and there is a homeostatic increase in parathyroid hormone levels with a consequent stimulation of bone resorption and accelerated bone loss (8). In elderly people vitamin D deficiency in common because the decreased exposure to sunshine and reduced capacity of the skin to synthesize vitamin D. Muscular strength is also regulated by vitamin D 13: lower than 25-30 nmol/l vitamin D status in older subjects is associated with muscular weakness, decreased physical performance and increased propensity to falls. On the other hand falls are considered one of the main risk factor for pathological fractures.

With the outcome to demonstrate the efficacy of calcium plus vitamin D to prevent the incidence of fractures many randomized controlled trials have been performed in the past two decades, with conflicting results. The daily oral dosage of calcium ranged from 500 to 1200 mg, and for Vitamin D from 400 to 800 IU. In general, more positive results in terms of fracture risk reduction or decrease of fall incidence were observed using Vitamin D 800 IU/day. The percentage of reduction of PTH levels seems to not correlate with antifracturative efficacy (9). A recent meta-analysis performed on 12 randomized controlled trials reports, together the correction of secondary hyperparathyroidism, a RR of 0.86 for non-vertebral fractures and a RR of 0.91 for hip fractures on eight trials, underlining the relationship between efficacy and the optimal dose of 800 IU/day of Vitamin D (10). As regards calcium intake, calcium supplementation is particularly important when baseline calcium intake is low. Besides Vitamin D, a crucial problem also for calcium supplementation is compliance and persistence: adherence with medication in osteoporosis is frequently less than optimal and this may modify treatment effect. In our opinion the use of calcium-dense foods could be encouraged to maintain adequate calcium intake across the lifespan. Considering that low calcium intake and poor Vitamin D status play a significant role to increase osteoporotic fracture risk, we believe that calcium and Vitamin D must be considered determinant components in the prevention of bone loss and falls, and in the treatment of osteoporosis together with antiresorptive or bone-forming agents.

A study performed in New Zealand in which calcium supplement was administered at the dosage of 1000 mg/day showed an increase in combined cardiovascular end-points compared with the placebo group (11). Particularly, myocardial infarction was more commonly reported in the calcium group than in the placebo group (45 events in 31 women vs 19 events in 14 women, $P=0.01$); the composite end point of myocardial infarction, stroke, or sudden death was also more common in the calcium group (101 events in 69 women vs. 54 events in 42 women, $P=0.008$). A subsequent meta-analysis confirmed that calcium supplements (without co-administration of vitamin D) are associated with an increased risk of myocardial infarction (12). The meta-analysis examined 15 trials: in the five studies contributing patient level data, 143 people allocated to calcium had a myocardial infarction compared with 111 allocated to placebo (hazard ratio 1.31, 95% confidence interval 1.02 to 1.67, $P=0.035$); non-significant increases occurred as regards the incidence of stroke. Moreover, in 11 trial level data similar results were appreciated: 296 people had a myocardial infarction (166 allocated to calcium, 130 to placebo), with an increased incidence of myocardial infarction in those allocated to calcium (rr 1.27, 95% confidence interval 1.01 to 1.59, $P=0.038$) (12).

The effects of personal calcium supplement use on cardiovascular risk were examined also in the Women's Health Initiative Calcium/Vitamin D Supplementation Study (WHI CaD Study). WHI CaD Study is a seven year, randomised, placebo controlled trial that analyzed 36 282 community dwelling postmenopausal women in which calcium and vitamin D were administered at the dosage of 1g and 400 IU per day, respectively (13). In the 16.718 women which represents the 46% of the population study, who were not taking personal calcium supplements at randomisation the hazard ratios for cardiovascular events with calcium and vitamin D ranged from 1.13 to 1.22 ($P=0.05$ for clinical myocardial infarction or stroke, $P=0.04$ for clinical myocardial infarction or revascularisation), whereas cardiovascular risk did not increase in the women taking personal calcium supplements at randomisation. The meta-analyses of three placebo controlled trials showed that calcium and vitamin D increased the risk of myocardial infarction (relative risk 1.21, $P=0.04$), stroke (1.20, $P=0.05$), and the composite of myocardial infarction or stroke (1.16, $P=0.02$). On the other hand, as regards meta-analyses of placebo controlled trials of calcium or calcium and vitamin D, complete trial-level data were available for 28 072 participants from eight trials of calcium supplements and the WHI CaD participants not taking personal calcium supplements: the number of subjects who experienced incident myocardial infarction or stroke was 1384, with an increased risk for myocardial infarction (relative risk 1.24, $P=0.004$) and for composite of myocardial infarction or stroke (1.15, $P=0.009$) in calcium or calcium and Vitamin D group. From these data the Authors conclude that calcium supplements with or without vitamin D represent a factor risk for cardiovascular events, especially myocardial infarction; at the same time, they underline that previous results of the Women's Health Initiative which reported no effect of calcium and vitamin D supplements on cardiovascular events, were obscured by the widespread use of personal calcium supplements at study entry. The conclusive remarks of the paper indicate that the use of calcium supplementation in osteoporosis management should be reassessed. However many questions remain on the table: is it sufficient a correct lifestyle to prevent bone fragility and fractures? May dietary calcium administration induce similar effect in maintaining bone mass as oral calcium supplementation? The beneficial effect of a correct calcium intake in attaining and maintaining bone mass across the life is largely demonstrated. May a small but significant adverse effect on cardiovascular risk in older age to obstruct the use of calcium in preventing osteoporosis?

The process of vascular calcification is a complex: it is possible that the increase in calcium supplements may influence vascular calcification by altering mechanisms that regulate calcification. Matrix vesicles are found in atherosclerotic calcification, along bone matrix proteins, such as osteopontin, osteocalcin, matrix GLA protein, and sialoprotein. Calcified lesions contain also osteogenic regulatory factors,

such as RUNX2, Osterix and Wnts. Calcium is a key cofactor in blood coagulation, and clot formation is a critical step in myocardial infarction, so subtle changes in the coagulability of blood following calcium ingestion could be involved (14). The calcium sensing receptor is also expressed in blood vessel walls, so changes in endothelial cells or smooth muscle cells might be important. On the other hand the process of arterial calcification is now recognised as being closely regulated by a number of inhibitors including pyrophosphate and fetuin-A. There is an urgent need for more research to gain insight into the mechanisms of the adverse vascular effect of calcium, since this might lead to strategies for circumventing it. Moreover, more extensive data about the incidence of cardiovascular adverse events coming from randomized controlled intervention trials in osteoporosis, in which calcium plus Vitamin D were utilized, might be achieved (15).

We believe that the role of calcium supplements in osteoporosis management must be definitively ascertained. Encouragement of dietary calcium intake is reasonable, since the balance of current evidence does not demonstrate a cardiovascular risk associated with calcium from food, although there is little compelling evidence that dietary calcium intake is associated with subsequent fracture risk. It is possible that calcium that dietary advice may be the appropriate way to attain an adequate calcium intake in most situations.

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