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# Calcium supplements: Good for the bone, bad for the heart? A systematic updated appraisal

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Calcium is the most abundant mineral in the human body. Approximately 99% of the total body calcium is present, in form of hydroxyapatite – a lattice-like crystal composed of calcium, phosphorus, and hydroxide – in bones and teeth, where it essentially plays a structural role. The remaining calcium is in the extracellular fluid and in various tissues, where it regulates numerous processes, including vascular tone, muscle contraction-dilation, nerve impulse transmission, intracellular signaling, ATP production, and hormonal secretion.

The physiological concentration of calcium in the blood is tightly regulated (Table 1) within a range of 8.8–10.4 mg/dL by parathyroid hormone (parathormone, PTH), 1,25-dihydroxyvitamin D3 (active metabolite of vitamin D), and calcitonin (CT). In order to maintain a normal calcium level, and to avoid conditions of calcium deficiency, the National Institutes of Health and the Institute of Medicine recommend a daily calcium intake of 1000

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mg for men aged 19–70 and women aged 19–50, to be increased up to 1200 mg for men aged 71 or older and women aged 51 or older.

## 1. Physiology of calcium homeostasis

In addition to conferring strength to the skeleton, the deposition of calcium in the bone represents a source of the cation when its serum concentration decreases: indeed, free calcium can be released through osteoclastic bone resorption. An unbalanced equilibrium between bone calcium deposition and resorption affects the bone mineral density (BMD) resulting in skeletal fragility. The leading actor in the regulation of this equilibrium and calcium homeostasis is vitamin D, which allows the intestinal absorption of calcium, favoring its storage through bone calcium deposition. When the serum calcium content decreases, the sensory receptors on parathyroid glands promote PTH release, which activates bone resorption to restore blood calcium and promotes Vitamin D activation, to indirectly support the absorption of calcium from external sources. If PTH is the main stimulator of Vitamin D synthesis, Vitamin D, in turn, inhibits PTH secretion [1,2]. A normal BMD reflects the proper functioning of this elegant mechanism.

During the physiological bone growth, when the calcium demand increases, or in pathological conditions characterized by defective calcium absorption, a higher calcium intake could be necessary to preserve BMD. However, the positive effects of calcium supplementation on skeleton fragility seem to be in contrast with the risk of side effects, such as cardiovascular events.

## 2. Impact of calcium supplements on the cardiovascular system

Although a balanced dietary intake of calcium and vitamin D is critical for our body in order to regulate critical mechanisms, the role of calcium and vitamin D supplementation in adults and elderly people remains not fully understood. In this issue of Atherosclerosis, Hulbert and colleagues show that calcium supplementation, but not dietary calcium, positively correlates with abdominal aorta calcification in postmenopausal women [3], suggesting that vascular calcification might contribute to the cardiovascular events observed in calcium supplement users. Several prospective cohort and randomized studies have demonstrated that an adequate calcium intake is associated with beneficial cardiovascular effects, including protection from hypertension, vascular disease, and stroke; moreover, calcium in association with vitamin D seems to be protective against coronary heart disease (CHD).

Based on these perceptions about calcium as a key component for the bone structure and critical for fundamental cellular processes, during the last decades we have observed a huge diffusion of calcium supplements and food enriched in calcium. Indeed, more than 50% of elderly men and almost 70% of elderly women in the US are considered regular users of calcium supplements.

## 3. Effects of calcium supplementation on BMD: results frommeta-analyses

Several clinical trials have tested the efficacy of calcium supplementation in children and adolescents, overall showing a positive effect of calcium introduction on BMD [4]. Instead,

it is not clear whether these effects are also detectable in the mature skeleton. One randomized clinical trial conducted in 354 females in the pubertal stage, examinated the long-time effects of calcium supplement on total-body BMD, from child to young adult [5]; the study revealed an increased BMD in the supplemented group at year 4, but this outcome vanished thereafter, supporting the hypothesis that calcium supplementation effects vary over time: calcium supplementation appears to influence bone accretion during pubertal growth spurt, losing most of the effects from young adult onwards.

In Western countries, the average calcium intake by diet is around 700–900 mg/day, which could be not enough to guarantee a proper BMD, especially in the risk population. Therefore, calcium supplementation has been proposed also for adult people and for the aging population to prevent or treat the pathological reduction of BMD that can lead to osteoporosis. To test the actual efficacy of this approach in preserving the BMD, various studies have been conducted and some meta-analyses well summarize the issue [6,7]. The first meta-analysis considered trials examining the effect of calcium supplementation on BMD and the risk of fractures in postmenopausal women showing a weak positive effect of calcium supplementation on BMD, with an increase of 2,05% of total body bone density after two or more years of treatment, respect to baseline [6]. This increase seems to have a rather low clinical relevance as it was associated with a reduced trend of the risk of experiencing only vertebral fractures (the risk was not reduced when evaluating non-vertebral fractures). Another meta-analysis considered the general population (men and women) aged over 50, including a total of 51 randomized control trials focused on calcium supplementation and changes in BMD [7]; overall, the analysis showed that calcium supplementation increases BMD by a maximum of 1,8%, starting from the first year of treatment without a progressive increase over time. Interestingly, this study indicates that the increase in BMD in response to calcium supplementation is of equal entity to what detected in response to calcium intake from diet. A meta-analysis that examined 33 randomized trials involving a total of 51,145 participants, demonstrated that the use of supplements that included calcium, vitamin D, or both compared with placebo or no treatment was not associated with a lower risk of fractures among community-dwelling older adults [8]. The most recent meta-analysis, assessing 6 ransomized-controlled trials of vitamin D combined with calcium *vs* placebo or no treatment shows that neither intermittent nor daily dosing with standard doses of vitamin D alone is associated with reduced risk of fracture; however, combined treatment with both vitamin D and calcium is associated with a 16% (95% CI, 3%–28%) reduction in the risk of hip fracture [9].

## 4. Calcium and vitamin D: friends or foes?

As mentioned above, calcium supplementation alone seems to have a minimum clinical impact in terms of risk of fractures. This outcome is not surprising if we consider that, especially in aged populations, a key issue is calcium absorption, due to a defective vitamin D bioavailability and/or activity. Indeed, vitamin D is the key regulator of intestinal calcium absorption; with aging, an increase of the enzyme involved in vitamin D catabolism occurs, alongside with a vitamin D resistence. Therefore, if a main problem is in vitamin D-dependent calcium absorption, the increase of calcium intake by diet or supplementation could not be adequate to overcome the insufficient intestinal absorbtion. In light of this

consideration, the addition of vitamin D to calcium administration should be more effective. Indeed, the effects of calcium supplementation on the risk of fractures is amplified by co-administration of vitamin D [10], particularly for hip fractures. In general, combining calcium and Vitamin D reduces by 10–20% the occurrence of non vertebral fractures [11]. Nevertheless, a recent trial has shown that daily supplementation with high-dose vitamin D does not result in a lower incidence of cardiovascular events or invasive cancer than placebo [12].

## 5. Calcium and cardiovascular risk: controversy even in meta-analyses; do we need more cowbell?

Most recently, some investigators started raising their eyebrows on this topic, because of the potential detrimental effects of high calcium intake (with or without vitamin D) on cardiovascular risk [13]. One of the principal mechanisms triggering major concerns in some researchers is the acutely increased serum calcium levels observed after calcium supplement intake; in fact, calcium intake from dietary sources does not seem to increase cardiovascular risk, while calcium supplements might raise CHD risk (Fig. 1).

Large observational studies have shown that augmented concentrations of serum calcium can increase the risk of myocardial infarction (MI), therefore it seemed logical to consider potentially dangerous to rise peaks of circulating calcium since this process can advance dangerous (ectopic) calcifications. Reid and collaborators reported that ionized calcium concentration increased from a mean of 1.22–1.30 mmol/L following supplementation with 1 g of calcium, either as citrate or as lactate gluconate [13]. Therefore, it is plausible that augmented plasma levels of calcium might alter the systemic balance in favor of calcification [13], which becomes a serious health risk when it occurs as ectopic calcification. The controversy on the actual role of calcium supplementation on cardiovascular risk has not been solved by meta-analyses (Table 2) of published studies, which have generated inconsistent results [14–21], showing how this important topic is debated and exposing the current uncertainty about optimal doses and regimens for supplementation and their overall effectiveness.

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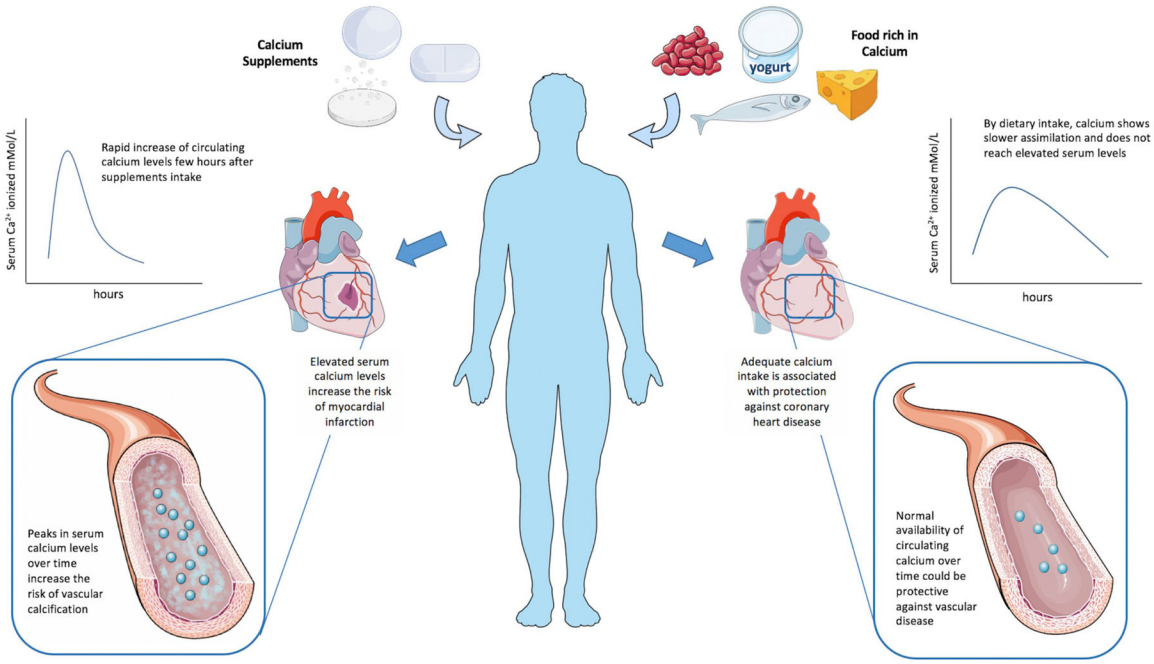


**Fig. 1.**

Calcium supplements rapidly increase circulating calcium and high levels of circulating calcium have been shown to increase cardiovascular risk; one of the possible mechanisms is the progressive ectopic calcification of the arteries, which could lead to coronary artery disease. On the other hand, dietary calcium intake has been shown to provide calcium via a slower assimilation, thereby allowing to maintain over time physiological calcium levels, a condition that seems to reduce the risk of cardiovascular disease.

**Table 1**

Normal values in adults.

| | Normal range (SI units) | Normal range (Conventional units) |
|---|---|---|
| Serum calcium | 2.2–2.6 mMol/L | 8.8–10.4 mg/dL |
| Ionized calcium[a] | 1.1–1.3 mMol/L | 4.4–5.2 mg/dL |
| PTH | 1.6–6.9 pMol/L | 15–65 pg/mL |
| Calcidiol, or 25-hydroxyvitamin D [25(OH)D][b] | 50–200 nMol/L | 20–80 ng/mL |

PTH: parathyroid hormone; SI: International System.

[a]Albeit all calcium in the body is technically ionized, the term usually only applies to the free ionic fraction that is physiologically active in the blood.

[b]In contrast to 25(OH)D, circulating calcitriol, also known as 1,25(OH)2D, is generally not a good indicator of vitamin D status because it has a short half-life of 15 hours and serum concentrations are closely regulated by parathyroid hormone, calcium, and phosphate; levels of 1,25(OH)2D do not typically decrease until vitamin D deficiency is severe.

**Table 2**

Meta-analyses assessing the association between DCSs or CSs intake (with or without Vitamin D) and cardiovascular events.

| Authors, Year | Meta-analysis for CHD, MI, CVD, and all-cause mortality | Total number of subjects | Ethnicity – Sex (age) | Follow –up (average or range of years) | Outcome | Ref. |
|---|---|---|---|---|---|---|
| Bolland et al., 2010 | 15 studies | 8151 (in 15 trials eligible for inclusion); plus 11,921 participants (in 11 trial level data) | Different ethnicity; males and females (from 51 to 77 years old) | Average of 3.6 years (15 trials for inclusion) and 4 years (11 trials level data) | In five studies contributing patient level data (5 studies), 143 participants allocated to calcium had an MI compared with 111 allocated to placebo (hazard ratio 1.31, 95% confidence interval 1.02 to 1.67, $p = 0.035$); composite endpoint of MI, stroke, or sudden death (hazard ratio 1.18, 95% confidence interval 1.00 to 1.39, $p = 0.057$), and death (1.09, 0.96 to 1.23, $p = 0.18$). The meta-analysis of trial level data (11 studies) yielded similar results: 296 participants had a myocardial infarction (166 allocated to calcium, 130 to placebo), with an increased incidence of myocardial infarction in those allocated to calcium (pooled relative risk 1.27, 95% confidence interval 1.01 to 1.59, $p = 0.038$). | 14 |
| Bolland et al., 2011 | 2 trials of co-administered calcium and vitamin D with CVD outcome data (WHI CaD Study), a small 1-year trial of 191 participants, plus previously unpublished data from two studies | 28,072 | Different ethnicity; only females (post-menopausal women) | Average 5.9 years | CSs with or without vitamin D modestly increase the risk of CVD events, especially MI. In meta-analyses of three placebo-controlled trials, calcium and vitamin D increased the risk of MI (relative risk 1.21 (95% confidence interval 1.01 to 1.44), $p = 0.04$), and the composite of MI or stroke (1.16 (1.02–1.32), $p = 0.02$). Meta-analyses of calcium or calcium and vitamin D complete trial-level data were available for 28,072 participants from eight trials of CSs and the WHI CaD participants not taking personal CSs. In total 1384 individuals had an incident MI or stroke. Calcium or calcium and vitamin D increased the risk of MI (relative risk 1.24 (1.07–1.45), $p = 0.004$) and the composite of myocardial infarction or stroke (1.15 (1.03–1.27), $p = 0.009$). | 15 |
| Rejnmark et al., 2012 | 8 studies for individual patient data; 24 studies for trial level data | 70,528 in the individual patient data; 88,097 in the trial data | Different ethnicity; males and females equal to 86.8% (with a median age of 70 years old, range, 62–77 years old) | Over 3 years | In participants randomized to treatment with vitamin D with or without calcium (OR, 0.95; 95% CI, 0.91–1.00) mortality was significantly reduced ($p = 0.04$). Stratification by coadministration of calcium showed reduced mortality in participants randomized to CaD (OR, 0.94; 95% CI, 0.88–0.99), but not in participants treated with vitamin D supplement alone. Influence analyses with the removal of studies one by one did not change risk estimates to any major degree. Restricting the trial level analysis to include only individually randomized doubleblind studies, mortality was reduced overall (OR, 0.94; 95% CI, 0.89–0.99). Stratification by coadministration of calcium showed a significantly ($p < 0.05$) reduced mortality in response to CaD (OR, 0.93; 95% CI, 0.86–1.00), but not with vitamin D alone (OR, 0.95; 95% CI, 0.89–1.03). | 16 |
| Wang et al., 2014 | 11 prospective studies with 12 independent cohorts assessing the association between DCIs and risk of mortality for CVD and all causes | For CVD study: 709,499; for all-cause mortality study: 225,189 | Different ethnicity; males and females (from 4 to 79 years old) | Large range: from 5.5 years to 28 years | Intakes around 800 mg/day conferred the lowest risk of cardiovascular mortality years Compared to individuals with 800 mg/day of DCIs, the predicted RRs for cardiovascular mortality were 1.08 (95% CI: 0.98 to 1.20) for individuals with 500 mg/day of calcium intake; 1.01 (95% CI: 0.98 to 1.04) for 1000 mg/day; 1.05 (95% CI: 1.01 to 1.09) for 1200 mg/day; and 1.10 (95% CI: 1.02 to 1.18) for 1400 mg/day years Compared to intakes of 900 mg/day, the risks of all-cause mortality comparing the highest and lowest level of dietary calcium intake was 0.83 (95% CI: 0.70 to 1.00; $p = 0.05$), with significant heterogeneity among the studies (I [2] = 74.9%; $p = 0.003$). | 17 |
| Asemi et al., 2015 | 21 prospective cohort studies and 1 nested casecontrol study | 2,346,368 | Different ethnicity; males and females (from 25 to 79 years old) | Large range: from 4.6 to 28 years | The studies revealed no significant association between total and dietary calcium intake and mortality from all-causes. Subgroup analysis by the duration of follow-up revealed a significant positive association between total calcium intake and CVD mortality for cohort studies with a mean follow-up duration of >10 years (relative risk (RR): 1.35; 95% confidence interval (CI): 1.09–1.68). A significant inverse association was seen between dietary calcium intake and all-cause (RR: 0.84; 95% CI: 0.70–1.00) and CVD mortality (RR: 0.88; 95% CI: | 18 |

| Authors, Year | Meta-analysis for CHD, MI, CVD, and all-cause mortality | Total number of subjects | Ethnicity – Sex (age) | Follow –up (average or range of years) | Outcome | Ref. |
|---|---|---|---|---|---|---|
| | | | | | 0.78–0.99) for studies with a mean follow-up duration of ≤10 years. Although supplemental calcium intake was not associated with CVD (RR: 0.95; 95% CI: 0.82–1.10), it was inversely associated with the risk of all-cause mortality (RR: 0.91; 95% CI: 0.88–0.94). | |
| Lewis et al., 2015 | 18 studies including 13 trials providing published data, and 5 trials providing unpublished data | 63,564 (3390 CHD events and 4157 deaths) | Different ethnicity; only females (post-menopausal women) | Large range: from 1 to 42 years | No analyses reached nominal levels of significance ($p < 0.05$) for any CHD outcomes. Five studies contributed data on CHD hospitalization and death in 48,460 women. 7.1% CHD events in the calcium with or without vitamin D group compared with 6.9% in the control group (pooled RR = 1.02, 95% confidence interval [CI], 0.96–1.09; $p = 0.51$). No heterogeneity between studies (I [2] = 0%). For CHD deaths were 1.3% in the CSs with or without vitamin D group compared with 21.2% in the control group (pooled RR = 1.04, 95% CI, 0.88–1.21; $p = 0.67$ with no heterogeneity [I2 = 0%]). No increased risk in CSs-treated patients for any secondary outcome (MI: RR = 1.08 [95% CI, 0.93–1.25; $p = 0.32$]; angina pectoris: RR = 1.09 [95% CI, 0.95–1.24; $p = 0.22$]; chronic CHD: RR = 0.92 [95% CI, 0.73–1.15; p = 0.46]). Little heterogeneity between studies for MI or angina pectoris (I [2] statistic = 8% and 0%, respectively). For CHD low heterogeneity (I [2] = 38%). | 19 |
| Chung et al., 2016 | 4 randomized trials, 26 prospective cohorts, and 1 nested case-control study examining the risk for CVD events or mortality in groups receiving placebo, CSs alone, or CSs plus vitamin D | 36,282 post-menopausal women, plus 1460 elderly women | Different ethnicity; only females (post-menopausal and elderly) | Large range: from 3 years to 30 years | The assessments of internal validity, precision of risk estimates, and consistency of results from studies, show that calcium intakes (from either food or supplement sources) at levels 2000–2500 mg/day are not associated with CVD risks in generally healthy adults. The analysis found a lower risk of HF with calcium and vitamin D supplementation in postmenopausal women without preexisting HF precursors at baseline (hazard ratio, 0.63 [CI, 0.46 to 0.87]) but no statistically significant effect of supplementation in those with HF precursors and conditions (hazard ratio, 1.06 [CI, 0.90 to 1.24]). Calcium plus vitamin D had no statistically significant effect on all vascular disease deaths compared with placebo (risk ratio, 0.99 [CI, 0.82 to 1.20]). No studies with significant effects of CSs alone on CVD outcomes (hazard ratios, 0.82 to 1.43). | 20 |
| Yang et al., 2019 | 42 studies including prospective cohort studies examining the association between DCIs/CSs and CVD, CHD, and MI | 1,222,041 | Different ethnicity; males and females (from 34 to 79 years old) | Average 9,9 years | Inverse relationship DCIs and CVD risk for duration ≤10 y (RR = 0.84; 95% CI, 0.72–0.98). No significant associations DCIs with CHD mortality or incidence (incidence: RR = 0.93, 95% CI, 0.83–1.05, I2 = 0.0%; for mortality: RR = 1.00, 95% CI, 0.91–1.11, I2 = 42.5%, P = 0.36). No association between CSs and risk of CVD (RR = 0.99; 95% CI, 0.93–1.05; $p = 0.74$) with a mild heterogeneity (I2 = 41.1%; $p = 0.12$). CSs with vitamin D did not increase the risk of CVD (RRco-supplementation = 0.99; 95% CI, 0.93–1.15; $p = 0.77$, I2 = 0). RCTs showed a risk of CHD due to CSs increased 8% (RR = 1.08; 95% CI; 1.02–1.22; I2 = 0.0%). Increased 20% due to CS alone (RR = 1.20, 95% CI, 1.08–1.33; I2 = 0.0%). Association between CSs and MI risk (RR = 1.14, 95% CI, 1.05–1.25; I2 = 0.0%). MI risk increased 21% with taking CSs alone (RR = 1.21, 95% CI, 1.08–1.35; I2 = 0.0%) | 21 |

CHD: Coronary Heart Disease, CSs: Calcium Supplements, DCSs: Dietary Calcium Supplements, CVD: Cardiovascular Disease, MI: Myocardial Infarction, WHI/CaD: Women's Health Initiative calcium-vitamin D supplementation.