# Calcium supplementation and vitamin D: a trigger for adverse cardiovascular events?

Editorial
Future Cardiology




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Calcium is an essential nutrient for human beings, relevant for bone strength, blood coagulation and as a second messenger in cells. Calcium supplements have frequently been prescribed for preventing or treating osteoporosis. Based on a recent meta-analysis from approximately 12,000 participants from 11 randomized controlled trials [1], calcium supplementation in osteoporosis management has been questioned. Results demonstrate that the risk of incident myocardial infarction in those patients allocated to calcium increased by 31%. In total, during an intervention period of 5 years, a total of 143 people allocated to calcium had a myocardial infarction compared with 111 people allocated to placebo.

Calcium supplementation only resulted in an increased risk of myocardial infarction in individuals with habitual calcium intakes above the median of 805 mg/day (hazard ratio 1.85, 95% CI: 1.28–2.67) but not in those with habitual calcium intakes below the median (hazard ratio: 0.98, 95% CI: 0.69–1.38, P for interaction 0.01). In many of the included studies, mean habitual calcium intake was already 800–1000 mg/day and therefore close to the recommended daily intake of 1000–1200 mg for adults [2]. Supplemental calcium intake was at least 1000 mg/day. Given the mean habitual calcium intake of 800–1000 mg/day, an inter-individual standard deviation in habitual calcium intake of approximately 500 mg/day, and the high amount of supplemental calcium, several patients in the calcium supplemented group may have exceeded the upper tolerable intake level for oral calcium, which has age-dependently been set to 2000 or 2500 mg/day for adults [2]. It is well known that above that intake level, soft tissue calcification such as vascular calcification can occur. Considering the high amount of total (habitual and supplemental) calcium intake of many individuals included in the aforementioned meta-analysis, the increased risk of myocardial infarction was not an unexpected finding (and should have been considered while planning the studies).

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In general, the connection between calcium and cardiovascular events is well established. Clinically, vascular calcification can cause thrombosis, arterial rupture and myocardial infarction. The presence of vascular calcification is also a predictor of a poorer 5-year survival rate in the general population [3]. Calcium deposits are found in almost all arteriosclerotic lesions and the process of vascular calcification is actively regulated. It is noteworthy that oral calcium results in a slight postprandial increase of blood calcium [4]. Importantly, only supplemental calcium but not dietary calcium seems to increase the risk of cardiovascular events [1], perhaps because supplemental calcium raises serum calcium in a more pronounced way than calcium ingested from foods, which may be absorbed more slowly. Altogether, available data demonstrate that calcium supplements should be prescribed with caution and only if habitual calcium intake is clearly below 1000 mg/day. Total (dietary and supplemental) oral calcium intake should not exceed 1000–1500 mg/day. On the other hand, it should also be noted that hypocalcemia (paradoxically) causes intracellular calcium overload, so calcium levels that are too high and too low can contribute to calcification and to cardiovascular damage.

**Keywords**
■ 25-hydroxyvitamin D ■ calcium ■ cardiovascular events ■ hypercalcemia ■ mortality ■ myocardial infarction ■ supplements ■ vascular calcification ■ vitamin D

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Calcium is closely linked to vitamin D, which is responsible for the calcium homeostasis of the human body. Vitamin D can increase intestinal calcium absorption from approximately 15 to 30% [5]. Together with calcitonin and parathyroid hormone, vitamin D homeostatically regulates serum calcium levels in a narrow range of 2.2–2.6 mmol/l. The risk of vitamin D-induced intoxication such as hypercalcemia (serum calcium > 2.6 mmol/l) can, however, not be excluded when circulating 25-hydroxyvitamin D (25[OH] D), which is the generally accepted indicator for assessing vitamin D status, exceeds approximately 372 nmol/l [6]. Several decades ago, it had already been demonstrated in animal studies, that supraphysiological amounts of vitamin D result in vascular calcification [7]. Moreover, the intermittently administered high doses of vitamin D, which had been used for the prevention of rickets in the former German Democratic Republic, have been made responsible for vascular calcinosis in childhood [8].

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However, the link between vitamin D and the risk of cardiovascular events is puzzling. Experimental studies also demonstrate that the active, hormonal form of vitamin D, 1,25-dihydroxyvitamin D, which is synthesized from its precursor 25(OH)D, down-regulates several negative pathways and up-regulates various protective pathways in the heart and vasculature [9]. Vitamin D supplementation improves serum triglycerides, pro-inflammatory cytokines, parathyroid hormone levels and flow-mediated dilation of peripheral arteries [10,11]. In line with these protective vitamin D effects, prospective cohort studies indicate an increased risk of fatal cardiovascular events at 25(OH)D levels below 25 nmol/l, a concentration which is frequently observed across western countries and among countries in the Middle East [12]. However, a very recent meta-analysis based on patient-level data indicates a 21% higher risk of myocardial infarction in calcium and vitamin D supplemented individuals compared with placebo administration [13]. Unfortunately, in that meta-analysis, important vitamin D-related data such as initial 25(OH)D levels, in-study differences in 25(OH)D levels between supplemented and placebo groups, and achieved 25(OH)D levels in the supplemented group, remained unconsidered, making it difficult to draw any definitive conclusion. Remarkably, a recent Cochrane data analysis came to the conclusion that vitamin D supplementation in the form of vitamin $D_3$ decreases all-cause mortality by 6% in predominantly elderly women who are mainly in institutions and who were dependent on receiving care [14]. Although the underlying mechanisms remain unclear at present, results should be included in strategies for improving human health and life expectancy.

Recently, the US-Institute of Medicine has declared that circulating 25(OH)D levels of 50 nmol/l are sufficient for the general population [2]. In addition, the US-Institute of Medicine has stated that for upper 25(OH)D levels sparse data are available and that values above 125 nmol/l should raise concerns among clinicians about potential adverse effects. The latter statement is at least partly based on a large prospective cohort study (National Health and Nutrition Examination Survey III) [15] indicating an increased multivariable-adjusted risk for all-cause mortality not only for 25(OH)D levels below 44.5 nmol/l but also for levels above 125 nmol/l. Nevertheless, it is also noteworthy that several vitamin D researchers recommend target serum 25(OH)D concentrations of at least 75–100 nmol/l and up to 250 nmol/l [16]. Moreover, the kind of the National Health and Nutrition Examination Survey III data interpretation concerning an increased mortality risk at 25(OH)D levels > 125 nmol/l has been questioned [17].

With respect to vitamin D status and cardiovascular events, it is also important to consider the interrelationship of physical activity. Compared with sedentary individuals, physically active adults have higher 25(OH)D and 1,25-dihydroxyvitamin D levels, and higher intestinal calcium absorption rates. Their mean daily calcium intake is approximately 2000 mg and thus also relatively high [18]. Note that physical activity is generally considered a preventive factor for cardiovascular disease risk [19], which can at least in part be explained by an altered calcium metabolism; acute physical activity is associated with a decrease in serum calcium. In physically active individuals, the surplus of absorbed calcium is partly deposed in the skeleton. In addition, a large amount is excreted via sweat [18]. Both mechanisms may prevent these individuals from vascular calcification. Notably, individuals with

frequent outdoor activities under sun-rich living conditions can have mean 25(OH)D levels of 135 to 163 nmol/l [20].

In conclusion, available data indicates that with respect to oral calcium intake, vitamin D status and cardiovascular events, it is important to consider the individuals' lifestyles and actual living situation. Calcium supplements should only be prescribed to frail elderly individuals. The patients should be at an increased risk of osteoporotic fractures. In addition, their dietary calcium intake should be clearly below 1000 mg/day without a foreseeable chance of a change in dietary habits. The calcium supplement should usually not exceed a daily dose of 500 mg. With respect to vitamin D, future studies are still warranted for a better clarification of the physiologic range of vitamin D for preventing cardiovascular disease. In the meantime, the following recommendations can be given: circulating 25(OH)D levels below 25 nmol/l are an urgent indication for improving vitamin D status (e.g., administration of a daily vitamin D supplement of 25 µg = 1000 international units), independent of the individuals' age. A similar dosed supplement can also be given to individuals with 25(OH)D levels between 25 and 50 nmol/l. In sedentary individuals with 25(OH)D levels in the range of 50 to 125 nmol/l there is, at present, no clear evidence for the need to increase or decrease 25(OH)D levels. Similar to vitamin D supplements, regular outdoor activities are able to improve vitamin D status, at least in the Summer half-year when sufficient ultraviolet B exposure guarantees the production of adequate amounts of vitamin D in the human skin. Physical activity also reduces the risk of cardiovascular disease. Regular physical activity may sometimes increase circulating 25(OH)D levels above 125 nmol/l. Presently, there is no evidence available demonstrating adverse effects on cardiovascular risk in this case.

**Financial & competing interests disclosure**

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*No writing assistance was utilized in the production of this manuscript.*

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