

COMMENTARY

Who should receive calcium and vitamin D supplementation?

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Abstract

Combined calcium and vitamin D supplementation is recommended in the prevention and treatment of osteoporosis. Until recently, supplementation was perceived as harmless without adverse effects. However, recent meta-analyses have provided evidence suggesting that calcium supplements, whether or not in combination with vitamin D, may be associated with cardiovascular risks. Although this finding constitutes a safety signal that has to be taken seriously, these data have to be interpreted with some caution. Current data do not allow definite conclusions to be drawn, but require further independent confirmation, since in numerous large studies, combined calcium and vitamin D supplementation did not increase cardiovascular events, even in the most frail and elderly populations. Nevertheless, it seems appropriate to correct calcium deficiency preferably by enhancing dietary intake and to target supplementation on individuals at high risk of fracture or in whom calcium and vitamin D deficiency is highly prevalent. Other trials have shown an increased risk of falls and fractures with annual oral administration of high dose of vitamin D. Therefore, supplementation with more frequent, lower doses is preferred. Yet, the optimal dosing schedule is unknown and needs further study. In order to correct age-associated secondary hyperparathyroidism and to prevent osteoporotic fractures, a daily dose of 1,000–1,200 mg calcium and 800 IU vitamin D is recommended in elderly or institutionalised people, patients with established osteoporosis and individuals on glucocorticoids.

Keywords: osteoporosis, calcium, vitamin D, dietary supplements, fracture prevention, cardiovascular complications, myocardial infarction

Calcium and vitamin D supplements in the prevention of osteoporosis and osteoporotic fractures

Numerous trials have convincingly shown that an inadequate intake of calcium and vitamin D is an important risk factor for the development of osteoporosis and osteoporotic fractures [1]. Vitamin D deficiency is common in older people, and together with a poor dietary calcium intake leads to negative calcium balance, which in turn

contributes to age-associated secondary hyperparathyroidism. As this is key in the pathogenesis of osteoporosis, calcium and vitamin D supplementation is generally recommended as the baseline therapy, as this has been shown to enhance bone mineral density and reduce fracture risk in both men and women, although the benefit may be reduced by poor compliance [2]. Vitamin D supplementation may also reduce the risk of falling, but only in a dose of at least 700 IU per day [3]. Trials that assessed the effect of calcium or vitamin D alone have failed to show a reduction in fracture risk [4, 5]. This is not surprising because the negative calcium balance in older people is often the result of low calcium intake and vitamin D deficiency. Supplementation therefore typically consists of

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combined supplementation with 1,000–1,200 mg calcium and 800 IU vitamin D [2].

Importantly, the inhibitory effects of calcium and vitamin D on bone resorption are short-lived and cease when supplementation is discontinued. Therefore, continued compliance and persistence with supplementation are essential to obtain therapeutic benefit.

Target populations for supplementation therapy

Large clinical trials have shown that generalised supplementation with calcium and vitamin D is not effective [6, 7]. Indeed, widespread supplementation implies the inclusion of people with a normal or marginally negative calcium balance. These individuals have a modest fracture risk and will not benefit from supplements. Hence, calcium and vitamin D supplementation should be targeted on individuals with a high risk of fracture and those documented with or at high risk of deficiencies.

In elderly (>75 years) or institutionalised people, calcium and vitamin D deficiency is ubiquitous [8]. In this group, trials have convincingly shown a lower risk of fracture with supplementation therapy [9]. On average, supplementation reduced the risk of non-vertebral fractures (including hip fractures) by 10–20% (Figure 1) [1].

Patients with osteoporosis benefit as well from calcium and vitamin D supplementation in addition to their osteoporosis medication. Randomised clinical trials with antiresorptives, which showed that these agents protect against osteoporotic fractures, were generally carried out on a background of calcium and vitamin D supplementation. Calcium and vitamin D supplementation is essential in patients on

osteoporosis medication, since deficiencies are common in these patients and supplementation therapy may enhance the effect of antiresorptive therapy [10].

Also patients on glucocorticoids, who generally have a negative calcium balance due to an increased urinary calcium excretion and a decreased intestinal and renal calcium absorption, need to embark on calcium and vitamin D supplements [11].

Calcium supplements and risk for myocardial infarction

A trial by Bolland *et al.* [12] suggested that calcium supplements might be associated with cardiovascular complications. The Auckland Calcium Study was a randomised, placebo-controlled trial in which almost 1,500 postmenopausal women were followed for 5 years. Exclusion criteria were osteoporosis medication, co-morbidity and low serum levels of vitamin D. Participants received 1,000 mg calcium/citrate or placebo. The analysis was set up to determine whether calcium supplements protect against cardiovascular diseases. After all, other trials showed favourable effects of calcium on lipid metabolism and blood pressure [13]. Moreover, observational research suggested an inverse correlation between dietary calcium intake and cardiovascular risk [14]. Unexpectedly, an increased cardiovascular risk was seen in the group that received calcium. In this group, the relative risk (RR) for myocardial infarction and stroke was 2.12 [95% confidence interval (CI) 1.01–4.47] and 1.42 (95% CI 0.83–2.43), respectively.

Since these results were based on small absolute numbers of events (34 myocardial infarctions and 57 strokes) which

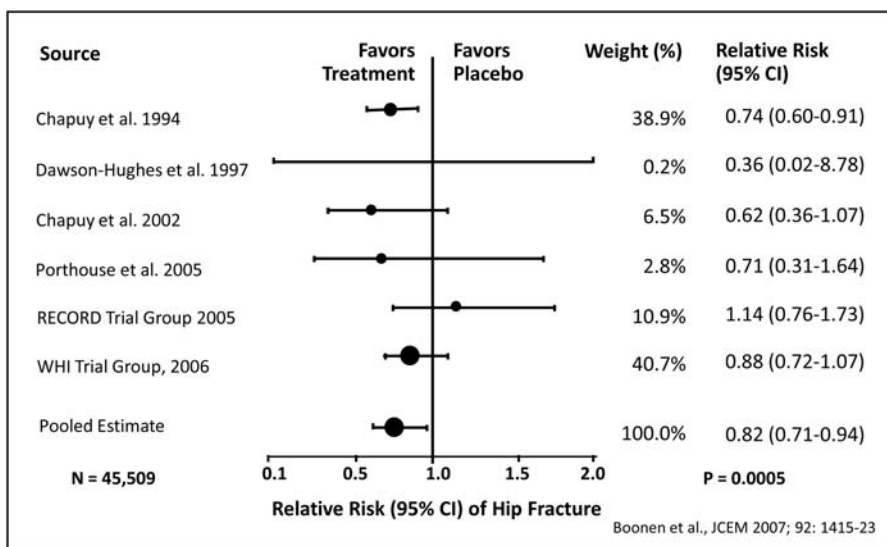


Figure 1. In fracture prevention, combination therapy with calcium and vitamin D is recommended. In a meta-analysis with more than 50,000 patients from randomised clinical trials, substitution therapy lowered the risk for hip fracture with 20%. The risk for other non-vertebral fractures was comparable in the active treatment and placebo group [1]. 95% CI, 95% confidence interval; N = number of study participants Figure reproduced with permission from ref. [1] (Copyright 2007, The Endocrine Society).

affected the study power, a meta-analysis was performed by the same authors. This meta-analysis included more than 12,000 individuals from 15 randomised placebo-controlled trials of calcium supplements (≥ 500 mg daily) [15]. An increase in the incidence of myocardial infarction of about 30% was seen in the calcium group when compared with the placebo group [hazard ratio (HR) 1.31, 95% CI 1.02–1.67]. No significant increases were observed in the incidence of stroke and the combined endpoint of myocardial infarction, stroke and sudden death.

Two studies dominated the meta-analysis: the aforementioned Auckland Calcium Study (relative contribution 17%) and the RECORD trial (relative contribution 55%) [6, 12]. The RECORD trial is a randomised placebo-controlled trial that failed to show a protection against osteoporotic fractures with calcium and vitamin D supplements. However, the result of this trial is inconclusive because of the low compliance with calcium and vitamin D (<40% after 24 months) and the fact that supplementation was not targeted on vulnerable people with calcium needs. In this trial, the incidence of death (17.7 versus 16.2%), myocardial infarction (3.4 versus 2.7%) and stroke (4.4 versus 3.9%) were comparable between the calcium and placebo group [6].

In a second meta-analysis of Bolland *et al.* [16], the cardiovascular risk of combined calcium and vitamin D supplementation was examined. This meta-analysis, which included three randomised placebo-controlled trials, showed that calcium and vitamin D significantly increased the risk of myocardial infarction (RR 1.21, 95% CI 1.01–1.44) and the composite endpoint of myocardial infarction and stroke (RR 1.16, 95% CI 1.02–1.32). The results of this meta-analysis are dominated by a re-analysis of the Women's health Initiative (WHI) clinical trial [16]. The original analysis of the WHI showed no adverse cardiovascular effect of combined calcium and vitamin D supplementation [7]. However, in the re-analysis that grouped participants according to whether or not non-protocol calcium supplements were used, calcium and vitamin D increased the risk of myocardial infarction or coronary revascularisation by 16% (RR 1.16, 95% CI 1.01–1.43) in the group without non-protocol use of calcium supplements. The risk of myocardial infarction (RR 1.22, 95% CI 1.00–1.50) and the combined endpoint of myocardial infarction and stroke (RR 1.16, 95% CI 1.00–1.35) increased non-significantly ($P = 0.05$) [16]. When the results of the two meta-analyses were combined, Bolland *et al.* [16] found that calcium alone or calcium and vitamin D increased the risk of myocardial infarction (RR 1.24, 95% CI 1.07–1.45) and the composite endpoint of myocardial infarction and stroke (RR 1.15, 95% CI 1.03–1.27).

The mechanisms by which calcium supplements might increase the cardiovascular risk remain speculative. Since high dietary calcium intake, which hardly affects serum levels of calcium, was not associated with an increased risk, the negative effect of calcium supplements might be explained by the fact that supplements acutely elevate serum calcium, which may enhance vascular calcification. Vascular calcification has been associated with an increased risk of cardiovascular

events in trials when calcium supplements were used as oral phosphate binders in chronic renal insufficiency as well as in the case of chronic hypercalcaemia caused by hyperparathyroidism. High serum calcium might also be associated with increased coagulability and arterial stiffness [17].

Calcium supplements: evidence in perspective

Although the meta-analyses of Bolland *et al.* constitute a safety signal that has to be taken seriously, some critical remarks have to be made.

First of all, the 31% increased risk of myocardial infarction in the first meta-analysis is a point estimate with a broad CI, compatible with either a 2% increase or a 67% increase in RR. The result was also only borderline significant ($P = 0.035$) [15], as was the case for the 21% increased risk of myocardial infarction in the second meta-analysis ($P = 0.04$) [16].

Secondly, the primary aim of the studies included in the meta-analyses was to examine the effects on bone strength and fracture risk. In none of these trials, cardiovascular events were registered in a standardised manner. These events were detected *post hoc* with varying criteria, which may have resulted in over- or under-reporting of myocardial infarction.

Thirdly, trials that combined calcium and vitamin D supplementation, the gold standard in the prevention and treatment of osteoporosis, were excluded from the first meta-analysis. The second meta-analysis did include three of such studies, but only one of these, the re-analysis of the WHI, was compatible with the overall result of the meta-analysis that calcium and vitamin D supplementation increase cardiovascular risk. Moreover, other large-scale studies of combined calcium and vitamin D supplementation that were not included in the meta-analysis did not document an increased risk of cardiovascular events [9, 18]. It is possible, but not proved, that vitamin D counteracts the detrimental effect of calcium.

Finally, it is important to stress that an elevated risk of myocardial infarction with calcium supplements was only observed in the trials of Bolland *et al.* [12]. Independent confirmation from other randomised clinical trials is lacking. In contrast, in a recent randomised placebo-controlled trial by Lewis *et al.* that was not included in the meta-analysis, the risk of death or first-time hospitalisation from atherosclerotic vascular disease was not higher in patients on calcium supplements. Further analysis even suggested that calcium supplements may reduce the cardiovascular risk in patients with pre-existing atherosclerotic cardiovascular disease [19].

Evidence against high-dose vitamin D

Also the safety of vitamin D supplements in the prevention and treatment of osteoporotic fractures has recently been questioned. In a recent trial, an annual high dose (500,000

IU) of oral vitamin D was associated with 15% more falls (RR 1.15, 95% CI 1.02–1.30) and 26% more fractures (RR 1.26, 95% CI 1.00–1.59) when compared with placebo [20]. *Post hoc* analysis showed an increased likelihood of falls and a similar temporal trend for fractures immediately after the administration of vitamin D. As expected, serum levels of 25-hydroxyvitamin D increased substantially 1 month after the administration and declined towards baseline thereafter, but remained about 40% higher than in the placebo group at 12 months [20]. The increased fracture risk might be explained by an acute increase in bone turnover markers, as was recently observed by Rossini *et al.* [21].

One other study reported an increased fracture risk associated with vitamin D [22]. In this randomised placebo-controlled trial, almost 9,500 men and women with a mean age of 79 years received an annual injection of 300,000 IU vitamin D or placebo. In women, but not in men, an increased fracture risk was seen at the hip or wrist (HR 1.59, 95% CI 1.17–2.16). No effect on falls was observed. In all other studies with a high dose of vitamin D, no adverse effects were reported.

Taken together, the safety of annual high-dose vitamin D supplements warrants further study.

Conclusion

To prevent osteoporotic fractures, combined calcium and vitamin D supplementation is recommended at the correct dosage (1,000–1,200 mg calcium and 800 IU of vitamin D per day). Supplementation should be targeted on vulnerable groups such as elderly and institutionalised people, patients with osteoporosis and individuals on glucocorticoids.

Numerous trials have shown that calcium and vitamin D supplementation is effective and safe. In particular, no increased cardiovascular risk was observed. However, recent data suggest that calcium supplements may be associated with cardiovascular risks and that annual high dose of oral vitamin D may increase the risk of falls and fractures. More evidence is needed to clarify the safety profile of calcium supplements as well as the optimal dosing schedule of vitamin D.

Funding

S. Boonen is senior clinical investigator of the Fund for Scientific Research (FWO-Vlaanderen) and holder of the Leuven University Chair in Gerontology and Geriatrics. This work was supported by grant G.0488.08 from the Fund for Scientific Research (FWO-Vlaanderen) to S. Boonen.

Conflicts of interest

The authors have no conflict of interest.

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Received 9 February 2012; accepted in revised form 28 May 2012