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Mini Review

Calcium Supplementation and the Risks of Cardiovascular Diseases

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Abstract

Studies related to calcium supplementation and effects on cardiovascular diseases are discussed. Results still being inconclusive, it is suggested in a recent review that future studies on calcium supplementation should be aimed at corroborating the level of dietary intakes of calcium with associated risks. As the amount of calcium supplementation varies from country to country, the average daily intake of calcium should be linked to the occurrence of cardiovascular diseases in order to arrive at a conclusion.

Keywords: Calcium supplementation; Cardiovascular diseases; CVD; WHI

Abbreviations

CVD: Cardiovascular Diseases; WHI: Women's Health Initiative

Introduction

Calcium containing compounds are one of the most popular non-prescription supplementation among peri or post-menopausal women as they are used to prevent osteoporosis and fractures. However, the protective role of excess calcium supplements (mainly calcium carbonate or calcium citrate) in the prevention of fractures or osteoporosis remains questionable and marginal [1]. The dilemma still continues on calcium supplements being a boon or a bane as there have been many reports though inconclusive on the risks associated with supplemented calcium, one of them being cardiovascular diseases.

Studies on calcium supplementation and CVD

Epidemiological studies warn that calcium levels at upper limits of normal appear to be associated with higher risk of cardiovascular events [2]. Supplementation may push serum calcium levels higher, further increasing the risk of cardiovascular disease, as deposition of calcium into the arterial wall can take place leading to atherosclerosis. Bolland et al. [3] observed that calcium supplementation increased myocardial infarction with an upward trend in stroke incidence. A meta-analysis of all trials in older adults randomly assigned to calcium or placebo for ≥1 year confirmed a 27% increase in the incidence of myocardial infarctions and again suggested an adverse effect on the risk of stroke [2]. Two subsequent meta-analyses [4,5] also found an increase in myocardial risk associated with calcium supplementation. These studies are in contradiction to the Women's Health Initiative (WHI) study wherein no adverse effect of calcium and vitamin D on cardiovascular health was observed [6]. The WHI differed from the study conducted by Bolland et al. [3] that participants already on calcium supplementation were also included in the trial and hence prior self administration might have obscured the adverse effects of calcium supplementation on cardiovascular disease risk. Bolland et al. [7] found that in subjects who were not already on calcium supplementation at the beginning of the study, calcium supplementation increased the risk of myocardial infarction and stroke. Addition of Vitamin D did not appear to have any effect on reducing the adverse effects of calcium. Higher death rates from cardiovascular disease (except stroke) have been noted with high intakes of calcium in women [8]. In a separate study, high intakes of supplemental calcium were found to be responsible for excess cardiovascular deaths in men [9]. The major pathophysiologic mechanisms include detrimental effects on vascular calcification [10,11]. Calcium raises fibroblast growth factor 23, which has been associated with higher levels of cardiovascular and all cause mortality. It also detrimentally affects vascular cells, plaque stability, platelet function and blood coagulation.

Many studies wherein there has been no association or no effect of calcium supplementation on cardiovascular diseases have also been reported. A meta- analysis of randomized controlled trials failed to identify any significant increases in the risk of cardiovascular diseases such as myocardial infarction, angina pectoris, and acute coronary syndrome following the use of calcium supplements [4]. In support of the lack of adverse cardiovascular effects following calcium supplementation, Lewis et al. [12] observed that daily supplementation with 1.2 g of calcium for 3 years did not increase carotid atherosclerosis in 1,500 older females who had a mean baseline calcium intake of 970 mg/day in both intention-to-treat and per-protocol analyses. Evidences that calcium supplementation enhances the risk of cardiovascular events is therefore inconsistent and inconclusive.

In a review article by Shin & Kim [13], the authors make an observation that the risk of cardiovascular diseases should be linked to the average daily intake of calcium. They suggest that risk in regions with low calcium intakes, such as East Asia, has yet to be determined. The average dietary calcium intakes in South Korea, Japan, China, Thailand, and other East Asian countries range between 300 and 500 mg/day [14] while, according to the Auckland and WHI studies, the average daily calcium intakes in New Zealand and the US are 800 and 850 mg, respectively. They point out that none of the nine studies included in the meta-analysis conducted by Bolland et al. [7] and the eighteen studies included in the meta-analysis conducted by Lewis JR et al. [4] utilized data from Asian countries or from individuals of other ethnicities except for one study (Thailand). The majority of these studies evaluated in these meta-analyses involved Caucasians from

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the US, the United Kingdom, France, Denmark, Australia, and New Zealand where the average dietary calcium intake ranges between 800 and 1,200 mg/day. This average is almost twice the calcium intake in East Asian or Central and South American countries. Therefore, whether or not approximately 1,000 mg/day of supplemental calcium would result in a similar risk of cardiovascular events in people with insufficient dietary calcium intakes remains unresolved from the authors' point of view.

Shin & Kim [13] further substantiate with studies that cardiovascular risk is associated with the levels of calcium intake. Michaelsson et al. [8] demonstrated in a study with Swedish population that the use of calcium tablets is associated with all-cause mortality only in individuals with a dietary calcium intake of >1,400 mg/day, however the mortality rates were higher among females with an intake of <600 mg/day, which resulted in a J-shaped relationship between calcium intake and mortality. The findings strongly suggested that the relationship between the risk of cardiovascular events and calcium supplementation was related to total calcium intake (dietary plus supplemental) rather than the use of calcium supplements per se. Based on this J- shaped curve, individuals already replete with a dietary calcium intake of up to 1,000 mg/day, such as in the US, New Zealand, and other Western countries, may have an increased cardiovascular mortality following supplementation with 1,000 mg of elemental calcium because their total calcium intake would have been approximately 2,000 mg per day [8]. Conversely, the authors argue that in individuals with a dietary calcium intake <500 mg/day, such as in East Asian countries, the risk of cardiovascular mortality would be decreased by increasing calcium intake via supplementation.

Further studies investigating the effects of supplemental calcium on cardiovascular events according to varied levels of dietary calcium intake are needed in order to get a clear understanding of the effect of calcium supplementation and cardiovascular risks. At present, there is not enough evidence to support the potential adverse cardiovascular outcomes that have been described by some studies. Shin & Kim [13] note that as dietary calcium intakes vary widely around the world, the effects of calcium supplementation are likely to differ according to specific dietary intake levels. Therefore, it would be reasonable to take dietary calcium intake into account when analyzing the risk-benefit profiles of calcium supplementation in different populations. They suggest that for individuals living in countries or regions with low calcium intakes, an appropriate regimen of calcium supplementation might be beneficial in terms of fracture prevention and the reduction of all- cause mortality. The authors conclude that studies aimed at studying the effect of calcium levels on cardiovascular risks in the future should collect population-specific data using subjects of different genders, ages, ethnicities, and risk profiles from different parts of the world to arrive at a definitive conclusion.

Conclusion

To summarize, adequate calcium intake remains an important concern in older adults and clarification of the population-specific antifracture benefits and cardiovascular safety of calcium supplements are important clinical and public health questions. Evidences supporting a causal relationship between supplementation and cardiovascular events remain inconsistent and inconclusive. Until additional data obtained from further studies are available, clinicians should promote adequate dietary calcium as a means to achieve the daily intake and supplements should be administered only to those subjects who do not have an adequate dietary intake.

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