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EDITORIAL

Calcium Supplements and Cardiovascular Disease Risk: What Do Clinicians and Patients Need to Know?

Calcium is the most abundant mineral in the body. Although 99% of total body calcium is found in the bones and teeth, it also plays an essential role in vascular contraction and dilation, muscle function, nerve transmission, intracellular signaling, and hormonal secretion (1). A recent comprehensive review convened by the Institute of Medicine (IOM) to establish population needs for calcium and vitamin D intake concluded that the scientific evidence was strong enough to support recommendations for intakes of these nutrients for bone health (1) but that the evidence related to extraskeletal outcomes was "inconsistent, inconclusive as to causality, and insufficient to inform nutritional requirements" (2). Thus, the IOM recommended that men and women aged 19 to 50 years consume a total of 1000 mg/d of calcium, and that women older than 50 and men older than 70 years consume a total of 1200 mg/d, emphasizing that there is no evidence that consuming higher amounts results in greater health benefits (1).

One area of particular controversy is whether calcium supplementation has adverse cardiovascular effects. This question is important, because many people consume calcium-containing multivitamin and mineral supplements. This topic began receiving attention in the past decade with the publication of 2 meta-analyses that suggested up to a 25% increase in the relative risk for myocardial infarction among study participants who received calcium supplements with or without vitamin D versus those who received a placebo (3, 4). However, several other high-quality meta-analyses reached different conclusions and found no consistent evidence from clinical trials or observational studies showing a link between calcium supplements and an increased risk for cardiovascular events (5–7). Furthermore, scant evidence exists for biological mechanisms linking calcium supplementation to atherosclerotic heart disease. A substudy of the Women's Health Initiative Calcium and Vitamin D trial found no difference in coronary artery calcium scores after 7 years in women receiving supplements (1000 mg of elemental calcium and 400 IU of vitamin D_3 daily) and those receiving a placebo (8).

Despite the seemingly robust volume of available literature on this subject (up to 18 studies with 64 000 participants in the largest meta-analysis), the evidence base has some limitations. None of the trials was designed primarily to evaluate the effect of calcium supplements on cardiovascular or coronary heart disease outcomes, increasing the potential for false-positive findings if several study outcomes are subjected to statistical testing without adjustment in the nominal significance level. This is particularly true when many secondary outcomes are evaluated in subgroup analyses, even if a theoretical justification might exist for such analyses (4). Because concerns about an increase in cardiovascular risk arose after most of the trials began, unpublished data on cardiovascular outcomes were collected and adjudicated retrospectively. However, outcome data from self-reports, hospital codes, and death certificates cannot be given the same weight as data from trials with rigorous ascertainment and adjudication methods, and "publication bias" may occur in this setting. Furthermore, many of the trials had poor long-term treatment adherence.

Given the limitations of the available evidence, can another systematic review and meta-analysis shed more light on the question of whether calcium with or without vitamin D supplementation affects cardiovascular disease risk? The new study by Chung and colleagues (9), commissioned by the National Osteoporosis Foundation, provides an update to the previous evidence reports on this topic (5, 10). In particular, the current study focuses on the published literature regarding the effects of calcium intake (from both dietary and supplemental sources) alone, because this aspect was not updated in the 2014 evidence report for the IOM dietary reference intake recommendations for calcium. The investigation by Chung and colleagues (9) breaks some new ground in its analysis of 27 observational studies. The authors used linear and nonlinear dose–response metaregressions to overcome a limitation that is particularly important in pooling studies of nutrients with widely varying intake levels in the reference groups. The results showed no consistent dose–response relationships between dietary or total calcium intake and risks for stroke, cardiovascular, or ischemic heart disease mortality, which were the most common outcomes reported by the studies.

Although the current report also summarizes clinical trial data, the authors state that they did not perform a meta-analysis, because the trials reported outcomes with heterogeneous definitions. The summary of the individual clinical trial data does not support an association between calcium supplementation and cardiovascular disease, with a statistically significant positive association for only 1 of 8 cardiovascular outcomes tested in the reanalysis of the Women's Health Initiative subgroup data (women not using personal calcium supplements at baseline) by Bolland and colleagues (4). However, only 4 separate trials are included in the summary, and the other analyses from the large-scale Women's Health Initiative showed no positive association between calcium and vitamin D supplementation and risk for coronary heart disease or stroke in the overall study population. The remaining 3 publications of calcium supplementation trials reported extended follow-up for cardiovascular outcomes, and none found significant associations with any outcome. Thus, the

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clinical trial data linking calcium supplementation to augmented cardiovascular risk is extremely limited.

How should clinicians and patients respond to the limited and imperfect evidence regarding the relationship between calcium supplements and cardiovascular risks? Although the preponderance of evidence does not support cardiovascular adverse effects, dietary sources of calcium are preferable to supplements for other reasons. Calcium supplements may increase kidney stone formation, whereas dietary calcium intake reduces the risk for kidney stones, a painful condition that affects 10% to 20% of adults (1). No evidence exists that consuming more calcium than the recommended dietary allowance will result in better bone health or any other health benefits. The median dietary calcium intake among U.S. adults (across all age–sex groups) is about 700 to 1000 mg/d, which may be attained by consuming 2 to 3 servings of high-calcium foods, including milk, yogurt, cheese, canned oily fish with bones, tofu, calcium-fortified juice, and leafy greens. Supplements may be used to make up but not exceed the gap between dietary intake and the recommended intake level; however, most persons require no more than 500 mg of supplemental calcium to meet their daily needs, if not met by diet alone. Achieving the recommended intakes of vitamin D (600 IU/d for adults up to age 70 and 800 IU/d for those aged 70 or older) also is essential (1). Based on the totality of evidence for both calcium and vitamin D, more is not better.

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