

Title: The Challenges of the Single Micronutrient Study

Commentary on Calcium Supplements and Cardiovascular Events

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Executive summary:

This review presents a position paper on behalf of the ASBMR Professional Practice Committee on the current controversy regarding calcium supplement use and the possible association with increased cardiovascular events. Data from randomized controlled trials, large cohort studies and three recently published meta-analyses are discussed.

While earlier publications reported a significant proportion of the adult population with very low calcium intakes, the 2010 NHANES report showed that a much greater percentage of people are meeting and some, in fact, exceeding daily-recommended intakes for calcium and vitamin D.

Recently, controversy has arisen based on reports of an increased risk of cardiovascular events associated with calcium supplementation. Publications with the opposing view that calcium supplementation does not increase cardiovascular events have also been recently published, including a meta-analysis and a randomized controlled trial with long term follow-up. This leads to the question of whether calcium supplementation is beneficial for bone but deleterious for the cardiovascular system.

Four recent publications, one a randomized controlled trial, one a prospective cohort study and two meta-analyses have suggested that there is an increased risk for adverse cardiovascular events in elderly adult men and women on calcium supplements. But, how convincing is the evidence for cardiovascular harm? The two “positive meta-analyses” use an unusual retrospective collection of patient level data, and select subpopulations of the original studies. A conventional and recent meta-analysis that included only original study data, in which compliance of >80% and outcomes were formally collected, reported no increase in adverse cardiovascular events. A RCT with an equivalent number of patients, nine and a half years of follow-up for cardiovascular outcomes and firm documentation of supplement compliance reported no evidence of increased adverse cardiovascular outcome. Several cohort studies found no evidence of cardiovascular harm.

The following lessons have come from this review: True placebo-controlled randomization in a trial of a single, readily available nutrient such as calcium is often difficult to achieve. Compliance with study parameters must be maintained, probably to levels well above 80% to provide confidence in a verifiable outcome, and it is important to monitor the intake of other dietary nutrients that might alter calcium effects. Clear, definable adjudicated endpoints must be utilized. The most appropriate and stringent methods of statistical analysis must be applied. Based on these criteria, the weight of evidence is insufficient to conclude that calcium supplements cause adverse cardiovascular events; however, the debate continues.

Abstract:

Summary This review presents a position paper on behalf of the ASBMR Professional Practice Committee on the current controversy regarding calcium supplement use and the possible association with increased cardiovascular events. Data from randomized controlled trials, large cohort studies and three recently published meta-analyses are discussed.

Introduction Bone is a living and dynamic tissue, which allows for continued growth and remodeling throughout life. Thousands of milligrams of calcium passively diffuse into and out of bone on a daily basis. Hundreds of milligrams of calcium are bioactively moved into and out of the bone matrix during cell-mediated bone remodeling. As much as 10,000 mg is filtered by the kidney each day with more than 98% of the filtered calcium being reabsorbed. Small increases in calcium efflux, such as minor increments in the renal filtered load over a prolonged period of time, can lead to chronic deficits in calcium balance. Inadequate dietary calcium can result in a negative balance with a compensatory loss of calcium from bone, a form of “negative spending” that can have detrimental consequences for skeletal integrity. During normal bone homeostasis, there are obligatory losses of calcium by the kidneys, GI tract and skin; replenishment via dietary intake is necessary to maintain a positive calcium balance.

Numerous agencies and organizations concerned with bone health have offered guidelines and recommendations for daily calcium intake. These recommendations are generally in agreement, but are directed at normal, healthy individuals. For example, the US National Academy of Sciences (NAS) in 1997 set guidelines of 1200 mg of elemental calcium as the recommended daily intake for adults over the age of 50 [1-4]. Nutritional surveys such as the National Health and Nutrition Evaluation Surveys (NHANES) 2003-2006 database documented that fewer than 10% of women up to the age of 70 and fewer than 1% after 70 years, along with fewer than 25% of adult men met the NAS guidelines for dietary calcium. When the 2003-2006 NHANES database was used to estimate calcium intakes from food, water, dietary supplements, and antacids for U.S. citizens, the estimated average calcium intakes from supplements in mg/day were as follows: for women aged 51-70, 578 mg/d; for women >71, 608 mg/d; for men 51-70, 268 mg/d; and for men >71, 372 mg/d [5]. Thus, calcium intake from the diet and all sources averaged over 1000 mg in all 4 groups (1186 in women 51-70; 1139 in women \geq 71; 1092 in men 51-70 and 1087 in men >71. Women relied on calcium supplements for about $\frac{1}{2}$ of their daily calcium intake. Men were more likely to get the majority of their intake from diet; with $\frac{1}{4}$ to $\frac{1}{3}$ of their total daily calcium intake derived from supplements. The differences between earlier NHANES reports and the current report on calcium intake in the United States [5] are important to take into consideration. While earlier publications reported a significant proportion of the adult population with very low calcium intakes, the 2010 NHANES report showed that a much greater percentage of people are meeting and some, in fact, exceeding daily recommended intakes. The increase in calcium intake is attributed to a greater intake of supplemental calcium; about 43% of the U.S. population and almost 70% of older females reported supplemental calcium use. With many people at or close to the Recommended Daily Intake and a greater percentage of the population exceeding these levels, it is important to consider both the benefits and the risks of supplementation.

The following websites are provided to inform about the general facts and recommendations for dietary intake.

(http://wwwn.cdc.gov/nchs/nhanes/bibliography/key_statistics.aspx)

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(http://www.nof.org/news/pressreleases/20100802-Calcium_Recommendations.htm),
(http://www.nof.org/prevention/BoneBasicsAlert_CalciumBasics.pdf),
(<http://www.surgeongeneral.gov/library/bonehealth/docs/OsteoBrochure1mar05.pdf>),
(<http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx>).
Individuals with impaired renal function, older persons, and individuals with gastrointestinal disorders with malabsorption, should consult with their physicians about the levels of calcium and other micronutrients intakes that are appropriate for them.

An important consideration relevant to calcium needs, is that the intake, absorption and metabolism of calcium are greatly influenced by the presence or absence of other micronutrients, especially in those individuals with low calcium intake. Calcium absorption is reduced in vitamin D insufficiency or deficiency. Another factor that modifies calcium metabolism in the United States is the often inappropriately large intakes of phosphate. Failure to consume these two key nutrients in equivalent amounts has deleterious effects on skeletal health. Nutritional surveys since 1990 have consistently documented that phosphate intake has exceeded calcium intake in adolescents and adults [2-4]. Furthermore, these surveys may significantly underestimate phosphate intake as they only record food intake and do not take into account food and beverage additives that are high in phosphate, [6]. In fact, it is estimated that on average, phosphate intake is always significantly higher than reported using simple food records [7]. If phosphate intake exceeds that of calcium, deleterious effects may be observed on bone metabolism. Animal studies consistently document the development of secondary hyperparathyroidism with bone loss in animals fed a phosphate rich diet, suggesting that the ratio of calcium: phosphate plays an important role in the negative effects phosphate can have on bone [8-11].

The “challenge of the “single nutrient clinical trial” lies in the many common confounders that potentially affect the outcome. Studies focusing on calcium as a micronutrient should make some effort to ensure that there is appropriate balance with other key nutrients that modulate calcium availability and effect. Unfortunately, studies on calcium supplementation seldom monitor for other key micronutrients that could modify calcium’s absorption or metabolism. Another common shortcoming of calcium supplementation studies is that they fail to monitor or report compliance and persistence of the recommended supplement. Failure to persist with assigned levels of calcium supplements is a severe challenge to the validity of a trial. All too frequently, the results of calcium supplementation trials are presented as though the changes, if any, are due to the designated calcium supplement alone. Finally, it is not entirely clear that data from single micronutrient supplement trials establish a basis for recommended daily intakes.

Recently, controversy has arisen based on reports of an increased risk of cardiovascular events associated with calcium supplementation [12, 13]. Publications with the opposing view that calcium supplementation does not increase cardiovascular events have also been recently published, including a meta-analysis [14] and a randomized controlled trial with long-term follow-up [15]. This leads to the question of whether calcium supplementation is beneficial for bone but bad for the cardiovascular system. Before we delve into the debate of potential harm, we need to weigh the reported benefits of calcium supplementation for improved bone health.

What effect does calcium have on bone turnover? A high bone-remodeling rate is frequently associated with bone loss and increased fracture risk [16]. Increased calcium intake at levels of 1000-2000 mg a day (achieved through supplements) was associated with a 10-20% reduction in the remodeling rate and corresponded to a 63-80% relative reduction in lumbar spine loss over a two year period [17] This effect was primarily seen in year one of supplementation, not in year two and may

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not be a persistent outcome. Interestingly, Aloia et al. [18] recently reported that calcium supplements decreased parathyroid hormone and bone resorption markers.

A trend toward an increase in bone density was seen with supplemental calcium. This data was summarized in a meta-analysis reported in 2002 that analyzed 15 clinical trials with a total of 1,806 postmenopausal women. While a positive effect on bone mineral density for total body, lumbar spine, and hip was found, the mean change of less than 2% did not achieve statistical significance. There was also a trend towards reduction in spinal fractures [[19]. Notably, this review was withdrawn from the Cochrane database of systematic reviews in 2007.

It has been claimed that calcium obtained from dietary sources is more beneficial than that obtained from supplements. While a balanced, healthful diet is important for overall well being, there are few studies that have compared dietary to supplemental calcium in a meaningful way. One study compared BMD changes at the trochanter in 168 subjects receiving placebo, milk powder or a standard calcium carbonate supplement for two years. Calcium supplementation by either the calcium tablets or the milk powder prevented bone loss in an equivalent manner [20].

Evidence that calcium supplementation reduces fracture incidence would in fact be the most convincing proof of skeletal benefit. The effect on fracture risk reduction with the use of calcium alone is small and most trials have not shown a statistically significant effect. Multiple meta-analyses have been conducted to evaluate the magnitude of the effect. Intent to treat analyses have failed to show an effect. Post-hoc analyses do show an effect of calcium on fractures in those patients who are compliant, but it is important to remember that post hoc analyses can introduce statistical biases. A meta-analysis [21] provided evidence from 17 trials with 52,625 subjects, in which there was a 12% risk reduction (RR equal 0.88, (CI of 0.83-0.95, $P < 0.0004$). The fracture risk reduction was even greater (a 24% reduction) when compliance was high (greater than 80%) and when calcium supplementation was equal to or greater than 1200 mg per day. However, only 6,517 subjects were in the calcium alone analysis. In this portion of the analysis, the RR was 0.9, with a CI of 0.8-1.0. The authors state that the addition of vitamin D to calcium did not change the treatment effect. An estimate of the Number Needed to Treat (NNT) was 63 patients for 3-5 years to prevent one fracture. This compared favorably to the NNT with regard to statins, where 40 patients treated for five years was required to prevent one major cardiovascular event. Both of the latter compounds fared better in this analysis as compared to the NNT for aspirin, which required 270 subjects treated for six years to produce the same cardiovascular outcome as a statin. Furthermore in elderly individuals on low dietary calcium intake, the NNT to prevent one fracture attributable to calcium supplementation alone was calculated to be as low as 30 [21].

What is the potential downside of calcium supplements? As previously stated, four recent publications, one a randomized controlled prospective trial, one a cohort study and two meta-analyses have suggested that there is an increased risk for adverse cardiovascular events in elderly adult men and women on calcium supplements. But, how convincing is the evidence for cardiovascular harm? To evaluate these data, Table 1 summarizes the meta-analysis of twelve randomized controlled trials of calcium supplementation versus placebo and Table 2 summarizes the five cohort studies presented by Bolland et al [13]. These studies represent the few large clinical trials of subjects followed or treated with calcium alone that report cardiovascular outcomes. As indicated in the annotation attached to the Tables, “patient level” data on cardiovascular events were not necessarily reported in the cited published studies. Rather, the data from the studies with superscripts were obtained post-hoc by Bolland et al by soliciting the data from the authors of those studies. As stated by Bolland et al “Cardiovascular outcomes were obtained from self reports, hospital admissions, and death

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certificates". Further, from Bolland et al 2010, these "patient-level" data were available on only 63% of the trial participants, and are reported to show an increased incidence ($p < 0.035$) of myocardial infarction with calcium supplementation, although the methods of ascertainment are unknown. These data did not reach significance for the conditions of stroke or the composite of myocardial infarct, stroke, or sudden death. As related in the modified Tables, all but one of the "non"-revised cohort studies [29] demonstrated a significant increase in relative risk (RR) for any specific cardiovascular outcome. One of the observational trials [28] found a significant trend in their cohort of 39,800 patients of a lower incidence of coronary heart disease as calcium supplementation increased from 0 to 1000 mg/day. One randomized controlled trial in elderly women reported an increased risk for a composite of three different end points, myocardial infarction, stroke and sudden death [12]. Each of these end points had different rates of occurrence and requires more stringent statistical analysis before the data can be used to produce a "combined" outcome. Such methods were not applied; furthermore, the data were based on a 60 % compliance rate [24, 12]. Another randomized controlled trial in a similar number of elderly women, examined more robust endpoints of cardiovascular death or hospitalization and used a proportional hazard time to first event analysis. This study had an 80% compliance rate and did not find an increased cardiovascular risk with calcium supplementation after five years of treatment [23] or in 4.5 years of follow-up [15].

While there are two recent meta-analyses on this important topic; they fail to bring closure because they come to opposite conclusions [14, 13]. There are many reasons to anticipate discordance from meta-analyses of the available data. First, there were differences in the studies selected. Most notably, The RECORD trial data [34] were excluded from the Wang meta-analyses [14] because by the selection criteria of Wang et al, the method of ascertainment of the cardiovascular endpoint(s) was not stated and compliance was not measured. Overall, and evident in Table 1, meta-analyses are difficult to achieve if the studies suffer from differences in the selected endpoints of stroke, death from ischemic heart disease, non-fatal myocardial infarction, or composite cardiovascular endpoints; and/or methods of ascertainment, self-report vs. hospital reports vs. death certificates, which are not always clearly or accurately recorded or subjected to the same or more stringent methods of validation. The study selection criteria of Wang et al excluded "studies that did not ascertain CVD events, including CVD death, nonfatal coronary heart disease (CHD) or myocardial infarction (MI), and nonfatal stroke." And did not include non-reviewed data collected often at long intervals after the original studies.

In the search for more data to help resolve the controversy, Bolland et al have recently published their analysis of a limited data set from the Women's Health Initiative (WHI)[39] placebo arm of the calcium supplementation study. In this post hoc analysis of a subset of patients who were not taking "personal calcium supplements", Bolland et al. reported increased relative risk of 1.24 (1.07-1.45) for MI and 1.15 for the composite outcome of myocardial infarct or stroke (sudden death was discarded). The P-values for these relative risk calculations were reported as highly significant. However as has been pointed out, this selected, post hoc subset analysis in which those subjects taking personal supplements were removed from the analyses undermines the randomization balance with respect to characteristics between groups. In the original publications by the WHI trial investigators (Jackson RD et al), multiple analyses failed to demonstrate increased cardiovascular risk [40]. In response to the Bolland et al. re-analysis, one of the original WHI investigators commented "exploratory reviews of past studies can often lead to findings that result from chance alone". Finally, as pointed out in an editorial on the recent Bolland et al study, several clinical trials and a retrospective study involving calcium plus vitamin D reported no increase in cardiovascular risk in the calcium plus D-supplemented patients [41]. The lively exchange of letters following the first Bolland et al "meta-

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analysis” can be reviewed in the British Medical Journal [42] and then followed by a more direct challenge by the major protagonists in a recent exchange of letters to the editors in JBMR [43]

The following lessons have come from this review: True placebo-controlled randomization in a trial of a single, readily available nutrient such as calcium is often difficult to achieve. Compliance with study parameters must be maintained, probably to levels well above 80% to provide confidence in a verifiable outcome, and it is important to monitor the intake of other dietary nutrients that might alter calcium effects. Clear, definable endpoints that can be validated must be utilized. The most appropriate and most stringent methods of statistical analysis must be applied.

Currently, the controversies over the long term safety of calcium (or calcium plus vitamin D) supplementation and cardiovascular health are not resolved. The stage is set for more debate. And so from which sources will the best answers come? Can data from RCT’s truly inform what is best clinical practice? Or, is there greater clinical utility in post-hoc analyses in large cohorts? Hopefully, more patient-level data that are fully transparent with regard to dose, duration, compliance, assurance that there is intake balance with regard to confounders such as phosphate, clear documentation of adverse events and application of appropriate statistical analyses may one day put these issues “to bed”.

Age, ethnicity and stages of the cycle were reviewed extensively in a recent summary of the Institute of Medicine Report [38]. Predominantly based on bone health data, data, the IOM set Recommended Dietary Allowances (RDAs) for $\geq 97.5\%$ of the population. Recommendations for calcium range from 700 to 1300 mg/d for life-stage groups starting at 1 year and continuing through the elderly. Although some clinicians may derive comfort from the exhaustive Institute of Medicine review of the literature, which considered adverse events as well as benefits, for many the debate still rages.

Disclosures:

RSB, CZ, DPK, RAA, declare no conflict of interest on any of the work in this manuscript.

After the completion of this position paper, C. Zapalowski became a full time employee of Amgen Inc. In accordance with the ASBMR’s Ethics Policy, Dr. Zapalowski resigned her position as a member of the ASBMR Professional Practice Committee upon her employment with Amgen Inc.

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Table 1. Randomized Controlled Trials (RCT):

Ref.	# Subjects	Ca dose	CV Endpoint	Control #	Calcium #	RR
[30]	361 women	0, 500	Stroke ^A	1	0	NA
[31]	135 women	0, 1,000	Stroke	1	2	NA
[32]	236 women	0, 1,600	Stroke ^A MI	0 0	0 0	NA NA
[22]	672-men 258 women	0, 1,200	CVD Stroke	46 11	50 12	NA.
[33]	262 men 154 women	0, 2,000	Stroke ^A	0	1	NA
[34]	774 men 4,498 women	0, 1,000	MI ^A Stroke ^A Composite ^A	73 106 175	89 116 197	NA NA NA
[26]	1,460 women	0,1200	CHD	51	56	1.12
[36]	563 women	0, 1,000	Stroke ^A	1	1	NA
[37]	734 women	0, 1,000 0, 1,400 or 1,500	MI ^A Stroke ^A Composite ^A	2 4 8	2 5 8	NA NA NA
[12]	1,471 women	0, 1000	MI Stroke Sudden Death Composite			1.49 (0.86-2.57) 1.37 (0.83-2.28) 0.51 (0.13-2.01) 1.21 (0.84-1.74)
[24]	323 men	0, 1200 600	Composite Death	0 1	3 2	NA
[15]	1,460 women	0, 1200	CV death or hospitalization			0.94 (0.69-1.28)

^A Patient Level Data provided to Bolland et al [13] by lead author, not in original citation

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Table 2. Prospective Observational Studies (Cohort studies)

Ref	Pt #	Ca amnt	CV-End Point (pt #)	Relative Risk-adjusted (CI)
[25]	43,738 men	0, >400	Stroke (328)	0.88 (0.6-1.27)
[26]	34,486 women	0, <500 >500	Isch Hrt Dis (387)	0.76 (0.58-1.0) 0.88 (0.64-1.23)
[27]	85,764 women	0, <,>400	Stroke (690)	0.88 (0.66-1.18)
[28]	39,800 Men	quintiles 0-1000	fatal CHD	0.87 (0.64-1.19) 1.02 (0.71-1.46) Trend for CHD 0.66 (0.34-1.1), p< 0.05
[29]	10,555 Women	supplement use yes/no	CHD (513)	1.24 (1.02-1.52)