COMMENTARY

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Calcium and vitamin D: To supplement or not?

We live in the era of evidence-based medicine, so new interventions must meet criteria for both safety and efficacy before they are adopted. However, we have inherited many practices adopted before the current standards were in place, and we have not always been rigorous in reevaluating traditional remedies. A conservative belief in established practice or the influence of vested interests may account for this lack of rigor in reappraisal.[1] Calcium and vitamin D supplements are possible examples of this phenomenon.

BONE METABOLISM IS TIGHTLY REGULATED

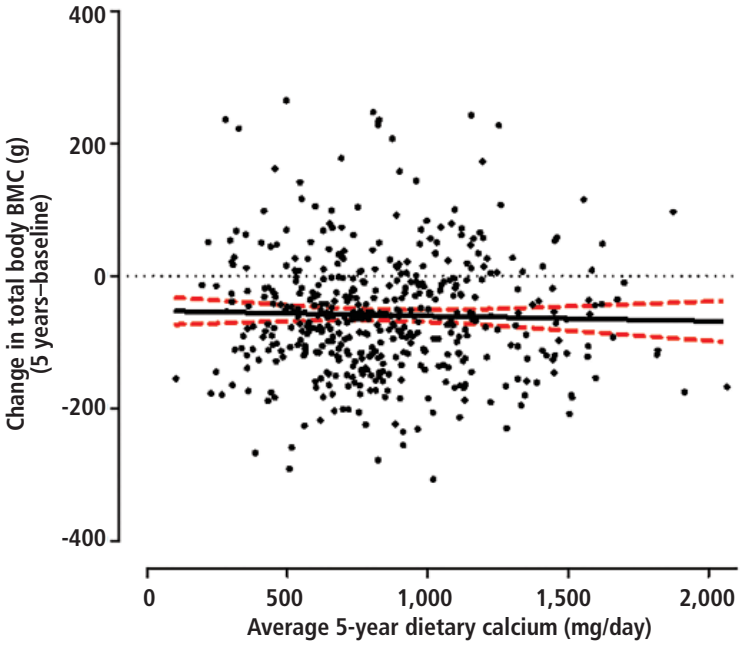
Bone is a connective tissue, its matrix composed principally of type 1 collagen, which provides tensile strength. Hydroxyapatite crystals, composed predominantly of calcium and phosphate, lie between the collagen fibers and provide compressive strength. In a tightly regulated process, osteoblasts lay down the collagenous matrix, and osteoclasts remove it. Mineralization of newly formed bone proceeds if normal levels of extracellular calcium and phosphate are present, in the absence of inhibitors of mineralization.

High calcium intake does not drive bone formation

The endocrine system is critical in maintaining normocalcemia. A decrease in calcium intake results in increased parathyroid hormone secretion, resulting in increased renal tubular calcium reabsorption, increased bone turnover (both formation and resorption), and increased activation of vitamin D leading to increased intestinal absorption of calcium. High calcium intake reverses these changes.

Thus, a normal serum calcium concentration can be maintained with calcium intake ranging from 200 to more than 2,000 mg/day, and rates of bone loss in postmenopausal women are unaffected by calcium intake (**Figure 1**).[2]

Calcium intake does not correlate with bone mineral content



Reid IR, Bristow SM, Bolland MJ. Calcium supplements: benefits and risks. J Intern Med 2015; 278(4):354–368.

Figure 1. Absolute change in total body bone mineral content (BMC) over 5 years in normal postmenopausal women, as a function of each woman's average calcium intake assessed at baseline and at year 5. The lines show the regression (with 95% confidence intervals) for this relationship ($P = .53$).

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If calcium intake is very low, hypocalcemia and secondary hyperparathyroidism develop,[3] and bone mineralization may be impaired. However, levels of calcium intake in Africa and in East and Southeast Asia are typically less than 400 mg/day,[4] yet there is no evidence that these levels adversely affect skeletal health. In fact, fracture risk is lower in these regions than in North America, where calcium intake is several times greater.

Thus, some calcium intake is required to maintain circulating concentrations, but there is no mechanism by which high calcium intake can drive bone formation. Quite the opposite, in fact.

Vitamin D deficiency has little relationship with diet

Vitamin D is a biologically inactive secosteroid activated by hydroxylation in the liver and kidney to function as the key regulator of intestinal calcium absorption. As with calcium, its deficiency results in hypocalcemia and impaired bone mineralization.

Paradoxically, high levels of vitamin D stimulate bone resorption and inhibit bone mineralization in mice,[5] and large doses increase bone resorption markers acutely in clinical studies.[6] Thus, it is important to ensure an adequate vitamin D supply, but not an oversupply.

Many traditional practices have not caught up with current evidence

In the absence of supplements, most vitamin D is produced in the skin as a result of the action of ultraviolet light (from sunlight) on 7-dehydrocholesterol. Thus, vitamin D deficiency occurs in those deprived of skin exposure to sunlight (eg, due to veiling, living at high latitude, staying permanently indoors), but it has little relationship with diet.

ARE CALCIUM SUPPLEMENTS EFFECTIVE?

Calcium supplements are certainly biologically active. They transiently increase serum calcium concentrations, suppress parathyroid hormone, and reduce bone resorption.[2] In the first year of use, they increase bone density by about 1% compared with placebo.[7] However, longer use does not result in further bone density advantage over placebo,[7] suggesting that the response simply reflects a decreased number of osteoclastic resorption sites and does not indicate a sustained change in bone balance.

A 1% difference in bone density would not be expected to reduce fracture risk, and a number of large, carefully conducted randomized controlled trials published over the last 15 years have failed to demonstrate antifracture efficacy for calcium.[8–12] As a result, the US Preventive Services Task Force recommends against the routine use of calcium supplements in community-dwelling adults.[13]

In contrast, in a placebo-controlled trial published in 1992, Chapuy et al[14] found that elderly women residing in nursing homes who received calcium and vitamin D supplements had fewer fractures. At 18 months, by intention-to-treat analysis, nonvertebral fractures had occurred in 160 (12%) of 1,387 women in the supplement group compared with 215 (15%) of 1,403 women in the placebo group ($P < .001$). However, these women were severely vitamin D-deficient (the mean serum 25-hydroxyvitamin D level at baseline in the placebo group was 13 ng/mL, normal range 15–50), to the extent that many must have had osteomalacia.

Thus, this study shows that calcium and vitamin D are effective in managing osteomalacia, but the subsequent trials[8–12] did not observe any benefit in community-dwelling cohorts. Meta-analyses that pool the Chapuy study with community-based studies generally find that calcium with vitamin D is beneficial, but the heterogeneity of these populations means that such pooling is inappropriate.[15]

It is sometimes stated that calcium and vitamin D should always be given with osteoporosis medications because the efficacy of these drugs has only been demonstrated when coadministered with these supplements. This is incorrect. The addition of calcium to alendronate does not alter its effects on bone density,[16] and the antifracture efficacy of both bisphosphonates[17] and estrogen[18,19] has been demonstrated in the absence of supplementation with calcium or vitamin D. The evidence that bisphosphonates prevent fractures in the absence of calcium supplements has recently been strengthened by the results of a randomized controlled trial comparing zoledronate with placebo in women over age 65 with osteopenia.[20]

ARE CALCIUM SUPPLEMENTS SAFE?

Calcium supplements often cause gastrointestinal symptoms, particularly constipation. They have been shown to double the risk of hospital admission due to abdominal symptoms.[21] In the absence of clear evidence of benefit, these facts alone should militate against their routine use. Calcium supplements also cause hypercalcemia and hypercalciuria[22] and increase the risk of renal calculi (by 17% in the Women's Health Initiative[8]).

Over the last decade, evidence has emerged that calcium supplements may also increase the risk of myocardial infarction, and possibly stroke. This finding was not statistically significant in any single study, but is consistently present in meta-analyses.[23]

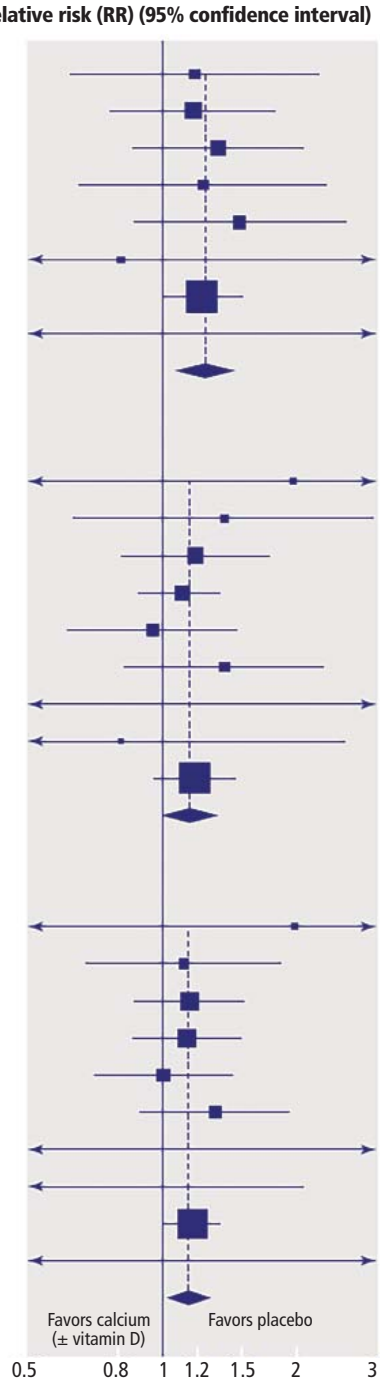
Evidence from the Women's Health Initiative

When studies of calcium with vitamin D are added to these meta-analyses, the results are less consistent. This is because such meta-analyses are dominated by the Women's Health Initiative (because of its large size, with 36,282 participants). There have been 2 different analyses of this trial with respect to cardiovascular events.

When the Women's Health Initiative as a whole was analyzed, there was no significant effect of calcium plus vitamin D on vascular end points. However, there is a significant interaction between body mass index and the effect of supplements, such that nonobese women demonstrated a 17% increase in myocardial infarction.[24] This study was unusual in that it included women already taking calcium and vitamin D supplements.

There was a significant interaction between baseline use of supplements and the effects of the trial intervention on vascular events, justifying analyzing the supplement-naive individuals separately. In this group of 16,000 women, an increase in clinical myocardial infarction of 22% was found, similar to the findings with calcium supplements alone.[25]

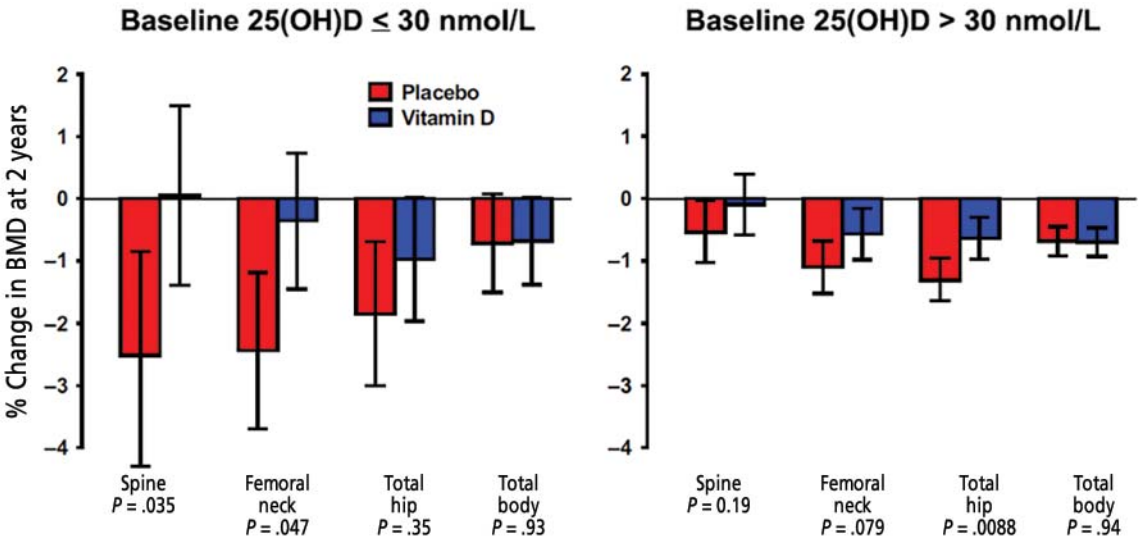
Thus, there is consistent evidence that introducing a calcium supplement de novo increases the risk of myocardial infarction (**Figure 2**).[16,25–31] We calculate that treating 1,000 patients with calcium or calcium plus vitamin D for 5 years would cause an additional 6 myocardial infarctions or strokes (number



Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ 2011; 342:d2040.

Figure 2. Effect of calcium supplements on cardiovascular events, with or without vitamin D. Data for 28,072 participants in 8 trials of calcium supplements with trial-level data, plus data for Women's Health Initiative CaD study participants not taking calcium supplements at baseline.

Vitamin D helps those who are deficient in it—others, not so much



Reid IR, Horne AM, Mihov B, et al. Effect of monthly high-dose vitamin D on bone density in community-dwelling older adults substudy of a randomized controlled trial. J Intern Med 2017; 282(5):452–460. Copyright 2017, The Association for the Publication of the Journal of Internal Medicine.

Figure 3. Changes in bone mineral density (BMD) from baseline to 2 years in the vitamin D and placebo groups of the Vitamin D Assessment study, according to baseline serum 25(OH)D (25-hydroxyvitamin D) concentrations. Data are mean ± 95% confidence intervals. *P* values are shown for between-group comparisons.

needed to harm 178) and prevent only 3 fractures (number needed to treat 302).[25]

Recent randomized trials have all failed to demonstrate antifracture efficacy for calcium

ARE VITAMIN D SUPPLEMENTS EFFECTIVE?

Vitamin D is highly effective in treating osteomalacia, improving symptoms within days and increasing bone density by as much as 50% over 1 year.[32,33] In contrast, randomized controlled trials of vitamin D supplements alone in people without osteomalacia have not shown increases in bone density or changes in fracture risk.[34–37]

In 2017, my colleagues and I published a trial showing that vitamin D supplementation increases bone density by 2% to 3% in the spine and femoral neck in participants with baseline 25-hydroxyvitamin D levels below 30-nmol/L (12 ng/mL), but those starting above this level showed no effect (**Figure 3**).[38] And a reanalysis of an earlier study confirmed this 30 nmol/L threshold for an effect of vitamin D on bone density.[39] The finding of a clear-cut threshold for vitamin D effects is predicted by the physiologic considerations set out above.

Belief that higher levels of 25-hydroxyvitamin D are better is based on observational data. However, correlation does not prove causation, and it is likely that causation is reversed here. Those with better health are likely to spend more time exercising outdoors, are less likely to be obese, and are less likely to have inflammatory conditions; and as a result, they are more likely to have better vitamin D status. We should now be using trial-based definitions of vitamin D deficiency as opposed to thresholds derived from disease associations in observational studies.

Vitamin D supplements have also been suggested to benefit cardiovascular health and to reduce cancer risk, though current clinical trial data provide no support for these hypotheses.[36,40] Other trials addressing these questions are ongoing.

ARE VITAMIN D SUPPLEMENTS SAFE?

The safety of vitamin D supplements has generally been assessed with respect to the incidence of hypercalcemia. On this basis, very high doses have been promoted. However, there is now evidence that doses of 4,000 IU/day, 60,000 IU/month, and 500,000 IU/year increase the risk of falls and fractures.[41,42]

The threshold for bone benefits discussed above (12 ng/mL) is easily exceeded with doses of vitamin D of 400 to 1,000 IU/day. At these levels, vitamin D supplements have no known adverse effects and can be widely endorsed for individuals at risk of deficiency. Supplement doses greater than 2,000 IU/day should be used only in exceptional circumstances, and with appropriate monitoring.

LITTLE USE FOR CALCIUM AND VITAMIN D SUPPLEMENTS

Extensive clinical trials have failed to demonstrate meaningful benefit from calcium supplements in the management of osteoporosis. Calcium supplements are often prescribed in patients who are receiving other treatments for osteoporosis, which may be justified with interventions that have the potential to cause hypocalcemia, but their coadministration with bisphosphonates has been shown to be unnecessary.

Calcium supplements commonly cause gastrointestinal symptoms that are sometimes severe and are likely to contribute to high levels of noncompliance with osteoporosis medications. They increase the risk of kidney stones,[8] and there is reasonable evidence to suggest an adverse effect on vascular risk as well.[23]

Vitamin D deficiency is common in frail elderly people, particularly those with dark skin or living at high latitudes. Low doses of vitamin D are safe and highly effective in preventing osteomalacia. But vitamin D supplements are unnecessary in those who regularly have sun exposure. And high doses of vitamin D have no demonstrated advantage and have been shown to increase the risk of falls and fractures.

Our decision to prescribe calcium and vitamin D supplements should be based on evidence that is of the same quality as for any other intervention we prescribe. Current evidence suggests that there is little reason to prescribe calcium, and that vitamin D should be targeted at those at risk of 25-hydroxyvitamin D levels less than 12 ng/mL.

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