ABSTRACT

Objective: To examine data showing associations between serum 25-hydroxyvitamin D levels and calcium intake and cardiovascular mortality.

Methods: The articles reviewed include those published from 1992-2011 derived from search engines (PubMed, Scopus, Medscape) using the following search terms: vitamin D, calcium, cardiovascular events, cardiovascular mortality, all-cause mortality, vascular calcification, chronic kidney disease, renal stones, and hypercalciuria. Because these articles were not weighted (graded) on the level of evidence, this review reflects my own perspective on the data and how they should be applied to clinical management.

Results: For skeletal health, vitamin D and calcium are both needed to ensure proper skeletal growth (modeling) and repair (remodeling). Nutritional deficiencies of either vitamin D or calcium may lead to a spectrum of metabolic bone disorders. Excessive consumption of either nutrient has been linked to a variety of medical disorders, such as hypercalcemia or renal stones. There have also been associations between vitamin D or calcium intake and cardiovascular disease. However, neither of these associations have established evidence nor known causality for increasing cardiovascular risk or all-cause mortality in patients with creatinine clearances greater than 60 mL/min. In patients with more severe chronic kidney disease, stronger data link excess calcium (or phosphorus) intake and increase in vascular calcification, but not mortality. The safe upper limit for vitamin D intake is at least 4000 IU daily and probably 10000 IU daily; for calcium, the safe upper limit is between 2000 to 3000 mg daily.

Conclusions: While no solid scientific evidence validates that serum vitamin D levels between 15 and 70 ng/mL are associated with increased cardiovascular disease risk, stronger but inconsistent evidence shows an association between calcium supplementation greater than 500 mg daily and an increase in cardiovascular disease risk. Most professional societies suggest that replacement levels of these nutrients be personalized with the goal of reaching a 25-hydroxyvitamin D concentration between 30 and 50 ng/mL and a calcium intake of 1200 mg daily. (Endocr Pract. 2011;17:pp)

INTRODUCTION

In the past few years, there has been a proliferation of publications on the effects of vitamin D and/or calcium on skeletal and nonskeletal health (1-2). While many of these articles have dealt with the nutritional requirements of vitamin D and calcium to define public policy (recommended dietary allowance [RDA] or dietary reference intake [DRI]) and population intake recommendations, many have examined the benefit–risk relationships of these 2 nutrients in altering the risk of cardiovascular disease.
In doing so, many—and often divergent—views have been expressed concerning the safety of vitamin D and/or calcium (8-10).

This review will try to put these issues into a perspective based on the best available science published to date, as well as the author’s perspective presented at an invited plenary lecture of the 2011 Annual Meeting and Clinical Congress of the American Association of Clinical Endocrinologists. This manuscript represents a systematic review of data from the search engines of PubMed, Medscape, and Scopus. The search words used were “vitamin D,” “calcium,” “cardiovascular events,” “cardiovascular mortality,” “all-cause mortality,” “vascular calcification,” “chronic kidney disease,” “renal stones,” and “hypercalcuiuria.”

Most of the evidence is derived from case-control and cohort population studies. Minimal data are derived from prospective, double-blind, placebo-controlled studies. The evidence is, therefore, limited by the nature of the study designs.

One question that must be examined: Are serum levels of 25-hydroxyvitamin D (25(OH)D) associated with an increase in cardiovascular mortality?

In humans, vitamin D is predominately derived from sunlight (ultraviolet) exposure (12-14). In periods of evolution, when humans wore few clothes or sunblock, sunshine was the dominant, if not the only, natural source of vitamin D. By changing skin 7-dehydrocholesterol to cholecalciferol, ultraviolet light is responsible for regulating serum levels of vitamin D. In this regard, even with the most intense and prolonged sunlight exposure, the maximum level of vitamin D that can be achieved is approximately 60 ng/mL. Hence, an internal homeostatic regulatory mechanism within the skin prevents serum vitamin D levels from rising above this value, which suggests that in the course of human evolution, there may have been reasons related to survival to explain why levels do not rise above 60 ng/mL (15-17).

The circulating vitamin D can enter the liver through the portal circulation to be taken up by hepatocytes, and the D is hydroxylated in the 25 position of the steroid backbone ring to produce 25(OH)D, the best measurement in clinical medicine of the adequacy of the nutritional replacement of vitamin D (18-20). Circulating D has its own direct effects on multiple tissues interacting with the vitamin D receptor alleles that are ubiquitous throughout human tissues. Here, 25(OH)D can increase the gastrointestinal absorption of calcium, influence mineralization of bone, and have effects on muscle cells—effects that are independent of its conversion in renal cells and macrophage-derived cells into 1,25-dihydroxyvitamin D (20-21). Circulating 25(OH)D also has an autocrine/paracrine pathway that is not as well understood as its endocrine function, but nevertheless, is also a very vital metabolic pathway for disposing 25(OH)D from the circulation. These latter 2 functions are related to the intracellular production of 1,25-dihydroxyvitamin D in many other cells that may regulate immune function and modulate cell survival in cancer cells (leukemia and breast and prostate cancer) within the cell in which 1,25-dihydroxyvitamin D is produced (autocrine) or in adjacent cells (paracrine) (20-22). The evidence supporting these autocrine/paracrine pathways effects of 1,25-dihydroxyvitamin D is stronger than the evidence for 25(OH)D per se on prevention of cancer (23). The remainder of the circulating 25(OH)D that is not stored in adipocytes or used intracellularly by way of 1,25-dihydroxyvitamin D pathways, is catabolized by 24-hydroxylase (20-22).

While there has been a great deal of recent controversy on the recommended intake of vitamin D, and it is not the purpose of this article to dive into this debate, a few points should be made concerning the recent publication of the Institute of Medicine (IOM) and how it might fit into the cardiovascular mortality story (1). The IOM recommends that persons aged 1 to 70 years receive 600 IU daily of vitamin D and persons older than 70 years receive 800 IU daily. While clinicians recognize that for individual patient management, the IOM vitamin D recommendations will fail to achieve a serum 25(OH)D level even above 20 ng/mL (the level suggested by the IOM), the good news is that the IOM recommendations do raise the RDA above the former RDA of 400 IU daily (24). In addition, to put the IOM work into perspective, this body of scientists was charged with making broad public policy (population) recommendations never intended to be applied to individual patient management. Individual patients often have other comorbid conditions (eg, gastrointestinal diseases, antiseizure medications) that increase their need for vitamin D, even to 5000 to 10000 IU daily, to maintain their 25(OH)D level above 40 ng/mL, the level recommended by the American Association of Clinical Endocrinologists and other scientific professional groups (25-26). In fact, the IOM itself said that the upper “safety” intake limit of vitamin D was probably 4000 IU daily and could be as high as 10000 IU daily. In addition, the large prospective placebo-controlled trial (Vitamin D and Omega-3 Trial [VITAL]) designed to examine the effect of vitamin D on the incidence of cancer and cardiovascular disease is using 2000 IU daily of vitamin D (27-28).

**VITAMIN D AND CARDIOVASCULAR MORTALITY**

The data on vitamin D and cardiovascular disease from a meta-analysis and a systematic review have been recently published (29-30) (Fig. 1). In addition, data have been published from additional systematic reviews: the Women’s Health Initiative, as well as the National Health and Examination Survey III (31-32). The conclusions from these analyses are that within the ranges of serum 25(OH)D measured, there is no solid evidence that vitamin D directly causes an increase in cardiovascular mortality. Although
findings from the National Health and Examination Survey III suggest that there may be a U-shaped curve where all-cause mortality is higher at lower or higher levels of serum 25(OH)D, the 95% confidence intervals overlap so widely that there is uncertainty about the importance of these findings. Even the IOM report states that the systematic survey of Cheung et al showed that with serum 25(OH)D concentrations less than 17 ng/mL and greater than 32 ng/mL there was no increased risk for cardiovascular mortality: “The RR was 0.97 (95 percent CI 0.92, 1.02), with no evidence for between-study heterogeneity (P=0.39, I^2 = 0 percent)” (30).

The phrase “vitamin D toxicity” is a misnomer, because there is no evidence that vitamin D has any direct tissue toxicity. So-called vitamin D toxicity is expressed through hypercalcemia due to an increase in gastrointestinal calcium absorption that exceeds the kidney’s capacity to excrete the extra calcium load or the bone’s capacity to deposit calcium via mineralization (33-34). These 2 tissues (kidney and bone) have an enormous ability to prevent hypercalcemia unless their ability to do so is compromised. For the kidney, this refers to function generally below a creatinine clearance of 30 mL/min where the clearance of calcium may not increase as the filtered load increases. For bone, this refers to adynamic bone disease where the very low bone turnover may mitigate the bone uptake of calcium (35-38). In the absence of compromised renal or bone function, the serum 25(OH)D level in most datasets must be greater than 150 ng/mL to induce hypercalcemia (39-40). Since it may take an excess of 10000 IU daily of vitamin D given for prolonged periods to induce a rise in the serum 25(OH)D concentration greater than 150 ng/mL, there is a wide safety margin in vitamin D administration. Likewise, hypercalciiuria does not seem to appear with vitamin D replacement less than 10000 IU daily (41-42). In non-calcium renal stone formers to begin with, there may be no increased risk for calcium stone formation with replacement of vitamin D less than 10000 IU daily (26,42). The issue may differ in persons who have previously formed calcium renal stones in whom the exacerbation of hypercalciiuria may increase the risk of calcium renal stone formation (43-44). The management suggestions for vitamin D pertain only to cholecalciferol and not to vitamin D metabolites (calcitriol, paracalcitriol) whose use is for different medical circumstances such as hypoparathyroidism, secondary hyperparathyroidism in chronic kidney disease, or specific oncology indications (45-49).

Hence, the American Association of Clinical Endocrinologists guidelines for vitamin D are clinically correct:

- To use 30 to 50 ng/mL for most patients as an optimal and safe range
- For many patients, 1000 to 2000 IU of vitamin D daily is required to maintain a 25(OH)D concentration at 30 ng/mL or above
Vitamin D, Calcium, and the Heart, Endocr Pract. 2011;17(No. 5)

- The common use of vitamin D in the range of 1000 to 2000 IU daily would be reasonable.

For now, it is important to use the recommendations in conjunction with clinical judgment to determine the proper calcium and vitamin D requirements for any given patient.

Endocrinologists, like many specialists, see patients who often have comorbid diseases that have competing effects on different areas of human body metabolism. More complex therapy must be managed on an individual case-by-case basis and cannot be set into algorithms that might be proper strategies for public policy decisions.

CALCIUM AND CARDIOVASCULAR MORTALITY

The IOM recommends the following for public policy (RDA/DRI) calcium intake (1): (a) 1200 mg daily for women aged 51 years and older and 1000 mg daily for men aged 50 to 70 years; (b) a “safe” upper limit of calcium intake of 2000 to 3000 mg daily. The IOM emphasizes that this total intake should include the consistent daily food consumption and added “supplements” to reach the RDA/DRI amount. To obtain this balance between nutrition and supplement, it is, therefore, incumbent that physicians complete a nutritional history on the patient. In addition, the nutritional intake used to calculate the prescribed daily calcium intake should be representative of typical intake. In this way, the physician becomes a nutritionist. This strategy may avoid the recommendations to “take 1000 mg daily” of supplements and ignore the nutritional contribution to total calcium intake. If there is any concrete evidence that calcium supplementation contributes to an increased risk for cardiovascular mortality, it is in the arena of excess calcium supplementation.

In this regard, the history behind the theme that calcium may be harmful to vascular tissue is derived from theories that excess calcium might act passively, complexing with phosphorus to be deposited in or on the endothelial surface of vessels and inducing vascular calcification. The evidence for vascular calcification from exogenous calcium sources is best seen in the renal world of patients with chronic kidney disease. Evidence has shown that in the populations with stage 3 to 5 chronic kidney disease (glomerular filtration rate <60 mL/min to <15 mL/min), and especially stage 5 (<15 mL/min on dialysis), calcium given as a calcium-phosphate binder to control hyperphosphatemia leads to an increase in vascular calcification (50-52). Data on an increase in mortality associated with this are, however, lacking. Although interventions to reduce the serum calcium and/or phosphorus in the setting of chronic kidney disease have also been associated with a reduction in vascular calcification, these interventions have not reduced cardiovascular mortality (53-55). Nevertheless, research is very abundant in this area in the chronic kidney disease population where the most common cause of mortality is cardiovascular disease, and direct causality might be established among chronic kidney disease, calcium and phosphorus intake, and mortality.

Associations have been reported between specific clinical disorders of calcium metabolism and an increased risk for cardiovascular mortality. Data have been published that suggest an association between hypercalcemia and increased mortality in healthy men and in patients with severe primary hyperparathyroidism (56-57). In the IOM report of data derived from their systematic analysis, the authors concluded that, “overall the majority of analyses showed no significant association between calcium intake and CV events” (1). However, the IOM found 1 cohort study (rated B for methodologic and reporting quality) that reported no significant associations between calcium intake and all-cause mortality in men or women aged 40 to 65 years. Only the Iowa Women’s Health Study of post-menopausal women showed a significant increase in cardiovascular death in those women with a mean calcium intake lower than 696 mg daily (58-59). The IOM reported that there “are no randomized controlled trials of calcium intake evaluated all-cause mortality.” The IOM may have undervalued recent systematic reviews, especially individual patient meta-analyses (7,9), which may have clinical and statistical advantages over trial-level meta-analyses (60-62).

New Zealand’s original study was an individual randomized controlled trial of 1471 healthy postmenopausal women, of whom one-half received 1 g of calcium as the citrate and one-half received placebo over a period of 5 years (6,10). The events were adjusted for baseline levels of vitamin D, body mass index, blood pressure, and fasting serum lipid levels. Persons with baseline vitamin D levels less than 10 ng/mL were excluded, in part because of the National Health and Examination Survey III data suggesting a higher cardiovascular mortality in this population with lower vitamin D levels. The results of the individual trial are shown in Table 1 (6,10). Findings from the primary and secondary analyses suggested a higher risk of the listed cardiovascular events in the calcium-supplemented group than in the placebo group. The Kaplan-Meier curves suggested that calcium supplementation had a greater negative effect on cardiovascular outcome the longer the duration of follow-up (Fig. 2) (6).

These observations led to a large meta-analysis of effect of calcium supplementation on risk of myocardial infarction and cardiovascular events (8). This analysis included postmenopausal women in trials that had a basic consistent inclusion for summary statistics: randomized, placebo-controlled, calcium supplement of 500 or more mg daily, more than 100 patients, mean age older than 40 years, and trial duration longer than 1 year. In addition, trials were excluded if the patients received only calcium or only vitamin D—they had to have received both calcium and vitamin D such that the placebo group had to also have...
received vitamin D. Finally, trials were excluded if patients had received calcium only as dairy or as a complex nutritional supplement (eg, multivitamin). The breakdown of the nature of this meta-analysis is shown in Table 2 (8).

The analysis of all cardiovascular outcomes is shown in Figure 3. For all outcomes, the relative risk favored placebo with confidence intervals that did cross 1.0. However, the relative risk of myocardial infarction favored placebo.

### Table 1
Individual Patient (Secondary) Analysis From the New Zealand Prospective Randomized Study of the Effects of Calcium Supplementation on Cardiovascular Outcomes (6,10)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Calcium, No. patients (No. events)</th>
<th>Placebo, No. patients (No. events)</th>
<th>Relative risk (95% confidence interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>143 (164)</td>
<td>111 (125)</td>
<td>1.32 (1.02-1.71)</td>
<td>.032</td>
</tr>
<tr>
<td>Stroke</td>
<td>167 (190)</td>
<td>143 (156)</td>
<td>1.24 (0.99-1.56)</td>
<td>.07</td>
</tr>
<tr>
<td>Myocardial infarction, stroke, or sudden death</td>
<td>293 (361)</td>
<td>254 (287)</td>
<td>1.27 (1.07-1.51)</td>
<td>.006</td>
</tr>
</tbody>
</table>

*a Kaplan-Meier survival plot for myocardial infarction showed the groups progressively diverged after about 2 years.*

### Table 2
Details of the Trials Included in the Meta-Analysis Examining the Effect of Vitamin D, Calcium, or Vitamin D and Calcium on Cardiovascular Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Duration, y</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies with individual participant cardiovascular outcome data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reid et al</td>
<td>135</td>
<td>4</td>
<td>Bone mineral density</td>
</tr>
<tr>
<td>Baron et al</td>
<td>930</td>
<td>4</td>
<td>Colorectal adenoma</td>
</tr>
<tr>
<td>Grant et al</td>
<td>5292</td>
<td>4</td>
<td>Low-trauma fracture</td>
</tr>
<tr>
<td>Reid et al</td>
<td>1471</td>
<td>5</td>
<td>Clinical fracture</td>
</tr>
<tr>
<td>Reid et al</td>
<td>323</td>
<td>2</td>
<td>Spine bone mineral density</td>
</tr>
<tr>
<td>Subtotal</td>
<td>8151</td>
<td>4.1</td>
<td></td>
</tr>
</tbody>
</table>

| Studies with trial-level cardiovascular outcome data          |                 |             |                             |
| Dawson-Hughes et al                                       | 361             | 2           | Spine bone mineral density  |
| Riggs et al                                                | 236             | 4           | Bone mineral density        |
| Bonithon-Kopp et al                                        | 416             | 3           | Colorectal adenoma          |
| Prince et al                                               | 1460            | 5           | Osteoporotic fracture       |
| Bonnick et al                                              | 563             | 2           | Spine bone mineral density  |
| Lappe                                                       | 734             | 4           | Fracture incidence          |
| Subtotal                                                   | 3770            | 3.8         |                             |
| Total                                                       | 11 921          | 4.0         | 93% of possible data        |

| Studies without cardiovascular outcome data                  |                 |             |                             |
| Smith et al, Elder et al, Recker et al, Peacock et al       | 922             |             |                             |

with confidence intervals that did not cross 1.0 (Fig. 4). When looking at the Kaplan-Meier curves in this meta-analysis, the data look similar to those of the initial single randomized trial—a greater risk over time in the calcium-supplemented group than in the placebo group (Fig. 5). The authors concluded that “calcium supplements increase the risk of CV events” and that “these results are robust because they are based on pre-specified end-points of randomized, placebo-controlled trials.”

In a counterpoint to the just-cited meta-analysis, the group from Western Australia completed a prospective, placebo-controlled randomized study of 1460 women (age 75 years) randomly assigned to CaCO₃ (1200 mg daily) or placebo (7,9). The study was a 5-year follow-up with a prespecified endpoint, and the data were adjusted for 13 known separate risk factors for cardiovascular disease. In
this study, there was no evidence that calcium supplementation increased the risk for cardiovascular disease. These authors believe that the New Zealand analysis included a substantial adjudication bias in that the myocardial infarctions were either self-reported or adjudicated, and they point out that when the Bolland et al individual trial data are reanalyzed, including only the adjudicated myocardial infarctions, the negative effect of calcium supplementation is less robust (Dr. Richard Prince, written communication, August 22, 2011). In addition, a forest plot (Fig. 6) shows the effect of using adjudicated data as opposed to the patient self-report data on risks of myocardial infarction from the studies reported by Bolland et al in their meta-analysis. The new data render the effect not significant (Dr. Richard Prince, written communication, August 22, 2011). These 2 opposing views are now hotly debated (63-65).

In addition, in a systematic review of literature published from 1996 to 2009 examining the effects of vitamin D and/or calcium on cardiovascular mortality from 17 randomized or cohort trials, there were no differences between calcium-supplemented and noncalcium-supplemented recipients (5). There is some concern over whether this latter study was underpowered to make the conclusions from the groups that only received calcium not combined with vitamin D.

The American Association of Clinical Endocrinologists osteoporosis guidelines suggest that the total calcium intake be 1200 mg daily and that this sum is achieved with diet and, when necessary, calcium supplementation. These guidelines have no comment on any association between calcium supplementation and cardiovascular risk.

**CONCLUSION**

Vitamin D measurements are important in skeletal health assessments. Persons may vary (because “it’s biology”) regarding the daily intake needed to achieve a 25(OH)D concentration of 40 ng/mL. No scientific data validate that a 25(OH)D concentration between 15 and 70 ng/mL has any increase in causality for cardiovascular mortality. Levels above the upper limit have not been adequately studied to make any conclusive statements. Scientific data suggest, but are inconsistent, that a specific calcium intake by supplements or serum calcium level has causality for an increase in cardiovascular mortality in the postmenopausal population. Public policy recommendations (RDA or DRI) differ from individual patient management recommendations, which must be accomplished on an individual patient level.

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DISCLOSURE

The author has no multiplicity of interest to disclose.

REFERENCES


