Osteoporosis and Fracture Risk Evaluation and Management

Shared Decision Making in Clinical Practice

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Fractures due to osteoporosis represent a serious and costly public health problem, leading to disability and increased mortality risk. For postmenopausal women, osteoporotic fractures are more common than stroke, myocardial infarction, and breast cancer combined. A fracture can be a life-changing event and may represent a significant threat to personal independence. Although osteoporosis is commonly defined as "a skeletal disorder characterized by decreased bone strength predisposing to an increased risk of fracture," it is fracture that is the important end result. A more pragmatic definition is "high risk of fracture, due at least in part to increased skeletal fragility." Primary care clinicians should be comfortable evaluating, preventing, and treating osteoporosis and related risks.

Skeletal fragility and high risk of fracture can occur at any age, in any race, and either sex but is more common in women than men and increasingly common with advancing age. A fracture with minimal or moderate trauma should lead to further evaluation. Fractures of the long bones (arms, legs), spine, and pelvis are associated with increased risk of future fractures, whereas fractures of fingers, toes, hands, feet, skull, or face (and possibly fractures of ribs, knees, elbows, and shoulders) are not. Other than fractures, there may be no signs or symptoms of osteoporosis. Therefore, a fracture risk assessment is necessary to identify people at risk.

Bone mineral density (BMD) measurement using dual-energy x-ray absorptiometry (DXA) is recommended for women at age 65 years and men at age 70 years in the absence of risk factors (other than age); however, a clinical fracture risk assessment should be performed around age 50 years (or earlier for women who undergo premature menopause) for risk factors: low body weight, early menopause (before about age 45 years), family history of osteoporosis, diseases (e.g., rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease), and drugs (e.g., glucocorticoids, proton pump inhibitors, selective serotonin reuptake inhibitors) that increase fracture risk. The presence of any of these factors would be reasons to order a bone density assessment sooner.

Adequate calcium, vitamin D, and exercise involving weight-bearing and resistance are important for bone health at any age and likely contribute to the effectiveness of medications to reduce fracture risk. The Institute of Medicine (now the National Academy of Medicine) recommends calcium intake of 1000 to 1200 mg/d, ideally from foods; calcium supplements may be needed for patients whose diets do not supply sufficient calcium. For vitamin D, 600 to 800 IU/d is recommended for public health purposes, but a supplement of 1000 to 2000 IU/d is reasonable for those at increased risk of osteoporosis; serum 25-hydroxyvitamin D levels higher than 30 ng/ml (to convert to nmol/L, multiply by 2.496) may be the appropriate target in such patients. Walking (or a weight-bearing "walking equivalent" such as treadmill or elliptical) for 30 to 40 minutes at least 3 times per week is ideal (5 sessions per week of aerobic activity is recommended for cardiovascular fitness; additional sessions, if needed could be non-weight bearing, such as swimming or cycling).

In addition to calcium, vitamin D, and exercise, patients at high risk of fracture should be offered medication to reduce fracture risk. The US National Osteoporosis Foundation recommends pharmacologic treatment for patients with hip or spine fractures thought to be related to osteoporosis, those with a BMD standard deviation of 2.5 or more below the young normal mean (T score, -2.5 or lower) and those with a BMD standard deviation between 1 and 2.5 below the young normal mean whose 10-year risk, using an online fracture risk calculator called FRAX, is 3% or more for hip fracture or 20% or more for major osteoporosis-related fracture (hip, humerus, forearm, and clinical vertebral fracture combined).

Before initiating pharmacologic treatment, laboratory studies should include measurement of serum calcium and creatinine. Antiresorptive medications are contraindicated if hypocalcemia is present and bisphosphonates, either oral or intravenously, should not be given if kidney function is reduced (i.e., glomerular filtration rate should be >30 or 35 mL/min). A complete blood cell count, chemistry panel, including serum phosphorus and 25-hydroxyvitamin D, also should be obtained to evaluate whether other health issues (such as hypercalcemia, multiple myeloma, liver or kidney disease, hypophosphatemia) require attention.

Four medications currently approved by the US Food and Drug Administration increase bone strength by
Box. Osteoporosis and Fracture Risk Evaluation and Management

Identification and Assessment
Identify patients with fractures from minimal or moderate trauma in adulthood to especially humerus, radius, femur, vertebra, or pelvis

In the absence of fracture, around age 50 years, ask about factors associated with increased fracture risk such as low body weight, early menopause, family history of osteoporosis, selected diseases and medications known to increase fracture risk (glucocorticoids, proton pump inhibitors, selective serotonin reuptake inhibitors).

Bone mineral density measurement using dual-energy x-ray absorptiometry (DXA) advised for women by age 65 years and men by age 70 years in the absence of risk factors but should be done sooner if someone has a significant fracture or one or more clinical risk factors.

When medications to reduce fracture risk are being considered, laboratory assessment is recommended (blood count, chemistry panel, 25-hydroxyvitamin D).

Management of Patients at High Risk of Fracture
At least 1 session devoted to patient education about osteoporosis, fracture risk, and medication choices.

Adequate calcium, vitamin D, and weight-bearing and resistance exercise.

Consider one of several pharmacologic agents to reduce fracture risk.

Oral options: alendronate or risedronate.

Nonoral options: denosumab, teriparatide, and zoledronic acid (consider referral to osteoporosis specialist).

Also identify and address nonskeletal risk factors for falling and fracture: problems with vision, hearing, balance, home safety adjustments, avoidance of floor rugs, etc.

Reassess progress periodically (every 1-2 years).

Treat with bone resorption. These include 2 oral bisphosphonates, nonoral weekly, or risedronate weekly or monthly (both available as generic products) and 2 nonoral agents, zoledronic acid (bisphosphonate) administered intravenously once yearly, denosumab (a receptor activator of nuclear factor kB-ligand inhibitor) administered subcutaneously twice yearly. These medicines have been shown to reduce the risk of spine, hip, and nonvertebral fractures.

For most patients in a primary care setting, an oral bisphosphonate is an appropriate first-line treatment. For other medications, patient consultation with an osteoporosis specialist may be helpful.

Although treatment to reduce fracture risk is a long-term proposition, bisphosphonates accumulate in bone; after a period of "loading," administration can be withheld for a "drug holiday" of at least 1 year or 2. Limited data suggest that patients at lower risk can start a drug holiday after 5 years of oral or 3 years of intravenous bisphosphonate treatment, whereas patients at higher risk should continue oral treatment for 10 years or intravenous treatment for at least 6 years.

The effects of denosumab are not sustained when treatment is stopped, so there is no drug holiday with this medication.

Other treatment options in selected cases include raloxifene, which reduces the risk of spine fractures but not hip or nonvertebral fractures but also reduces the risk of breast cancer, and teriparatide, which as anabolic agent has a different mechanism of action from the other agents and is usually reserved for patients whose osteoporosis is unusually severe or who are not responding to other therapies.

Repeating DXA after 1 to 2 years of treatment and periodically after that is useful for monitoring treatment.

If bone density decreases or a fracture occurs, the patient should be reevaluated and treatment options reconsidered.

Patient understanding is important for acceptance of and adherence to treatment. Likely this will require at least 2 visits with the physician and health care team. The first visit involves starting the process with a fracture risk assessment and, if appropriate, an order for DXA measurement. The second, which should occur shortly thereafter, involves discussion of the results and development of a management plan that is acceptable to the patient. Sample patient information material is available and may be helpful to provide to patients.

For diseases in which patients are asymptomatic, adherence to treatment to reduce risk of future adverse events is poor. With some treatments for osteoporosis, publicity about rare but concerning safety issues (osteonecrosis of the jaw, atypical femur fractures) has contributed to lack of acceptance or continuation of treatments. Understanding patients' decision making and providing accurate information—that in most cases, benefits of treatment far outweigh the risks—are essential for optimal long-term management of this potentially serious disorder.

REFERENCES

**VITAMIN D, CALCIUM, AND CARDIOVASCULAR MORTALITY: A PERSPECTIVE FROM A PLENARY LECTURE GIVEN AT THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLISTS**

**Paul D. Miller, MD**

**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 hypercalcemia. 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)

**Abbreviations:**

\[25(OH)D = 25	ext{-hydroxyvitamin D}; \text{DRI} = \text{dietary reference intake}; \text{IOM} = \text{Institute of Medicine}; \text{RDA} = \text{recommended dietary allowance}\]

**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 non-skeletal 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
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, I² = 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, hypercalcitria does not seem to appear with vitamin D replacement less than 1000 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 hypercalcitria 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
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</th>
<th>Placebo</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>

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

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).

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>
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<tr>
<td>Subtotal</td>
<td>8151</td>
<td>4.1</td>
<td></td>
</tr>
</tbody>
</table>

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

Studies without cardiovascular outcome data

Smith et al, Elder et al, Recker et al, Peacock et al

Subtotal 922

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.

**ACKNOWLEDGMENT**

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