

# Bone health<sup>1-3</sup>

Robert P Heaney

## ABSTRACT

Much evidence indicates that both calcium and vitamin D are efficacious in protecting the skeleton, particularly when these 2 nutrients are used in combination. Each nutrient is necessary for the full expression of the effect of the other, and where their actions are independent, their effects on skeletal health are complementary. Nutrient status for both tends to be deficient in the adult population of the industrialized nations. Hence, supplementation or food fortification with both nutrients is appropriate and, given contemporary diets and sun exposure, probably necessary. Various meta-analyses, systematic evidence reviews, and controlled trials evaluating these 2 nutrients will be defective if they fail 1) to take into consideration the nearly universal need to augment the status of both nutrients in the populations studied rather than just one or the other, 2) to consider the threshold characteristics of both nutrients, and 3) to use the achieved serum 25-hydroxyvitamin D concentration as the independent variable for vitamin D effects (instead of oral vitamin D intake). Problems with adherence to a regimen of taking supplements daily make an appropriate fortification strategy the preferred option for improving the status of both nutrients. *Am J Clin Nutr* 2007; 85(suppl):300S-3S.

**KEY WORDS** Calcium, vitamin D, fractures, falls, bone health, supplementation, fortification

## INTRODUCTION

Of the nutrients generally included under the heading *multi-vitamins and minerals*, the 2 most directly related to bone health are calcium and vitamin D. In evaluating evidence relating to their efficacy, it is important that they be considered together. This is because each needs the other for certain of its actions and, where they function independently, each complements the other with respect to various bone health endpoints. Meta-analyses or other systematic evidence reviews that analyze studies of the 2 nutrients separately, and especially those that exclude studies testing the combination, are likely to produce misleading conclusions (1-3).

## CALCIUM AND VITAMIN D—A PARTNERSHIP

A large body of evidence, reviewed extensively elsewhere (4-10), indicates that supplementing calcium and vitamin D has positive effects on both health. Specifically, these nutrients enhance bone gain during growth, reduce age-related bone loss, and reduce fragility fractures, particularly in the elderly and probably in adolescents as well. Such outcomes are plausible in view of the fact that roughly 85% of the female population after childhood

fails to get the recommended intake of calcium, and, depending on the age and population group studied, from 65% to nearly 100% of the population after mid-life has a serum 25-hydroxyvitamin D concentration [25(OH)D] <80 nmol/L (which many lines of evidence suggest may be the lower limit of the healthy range).

Hence, consideration of nutritional supplementation is appropriate, not only at an individual level, but also at a population level. The Surgeon General, in his *Report on Bone Health and Osteoporosis* (9) stated "Calcium has been singled out as a major public health concern today because it is critically important to bone health and the average American consumes levels of calcium that are far below the amount recommended for optimal bone health."

Because calcium and vitamin D, administered together, have been shown to reduce fracture risk in randomized controlled trials and because those studies have been incorporated into existing policy statements (4-9), I will not present that evidence again here. It may be more useful to look at the mechanisms by which the 2 nutrients produce their beneficial effects. Understanding these mechanisms may provide useful insights on how both to enhance and to evaluate efficacy. With reference to skeletal health specifically, both calcium and vitamin D act in 2 distinct ways: by offsetting obligatory calcium losses from the body and by reducing excessive bone remodeling.

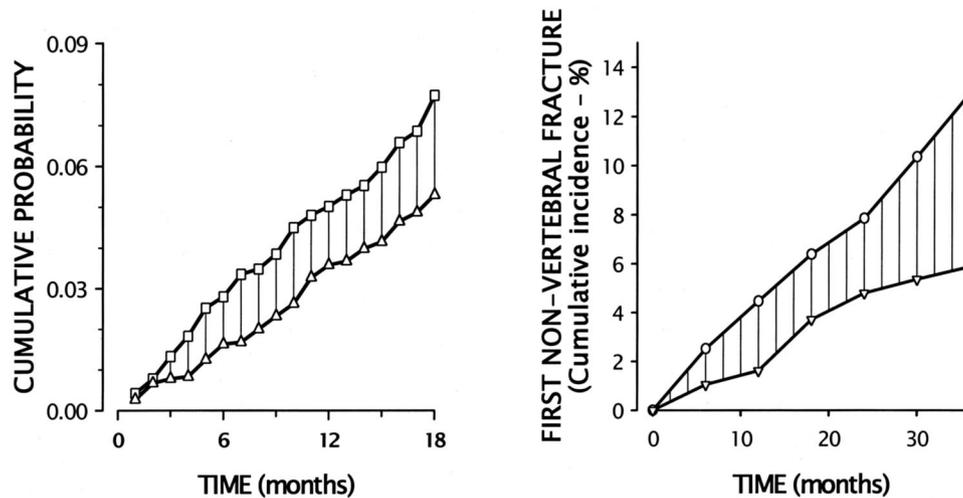
## OFFSETTING OBLIGATORY LOSSES

The initial conceptual framework relating calcium and vitamin D to bone health centered on the fact that obligatory losses of calcium from the adult human body are relatively high and calcium absorption efficiency is relatively low. This creates a need both to have a high calcium intake and to absorb it with reasonable efficiency. To protect extracellular fluid [ $\text{Ca}^{2+}$ ] when absorbed calcium is not sufficient to offset obligatory losses, bone will be torn down to scavenge its calcium. In this arrangement, a high calcium intake is important because it is the bulk input needed to offset corresponding outputs. Vitamin D is important because it is necessary for efficient absorption of calcium from the diet. This conceptual framework remains essentially

<sup>1</sup> From Creighton University, Omaha, NE.

<sup>2</sup> Presented at the conference "Multivitamin/Mineral Supplements and Chronic Disease Prevention," held at the National Institutes of Health, Bethesda, MD, May 15-17, 2006.

<sup>3</sup> Reprints not available. Address correspondence to RP Heaney, Creighton University Medical Center, 601 North 30th Street, Suite 4841, Omaha, NE 68131. E-mail: rheaney@creighton.edu.



**FIGURE 1.** Plots of the cumulative incidence of fractures, redrawn from the studies of Chapuy et al (17) (right) and Dawson-Hughes et al (18) (left). In both cases, the upper line represents the placebo control subjects and the lower line represents the subjects treated with calcium and vitamin D. The shaded zones represent the reduction of fracture risk, which, as can be readily seen, starts with the beginning of treatment. (Copyright Robert P Heaney, 2004. Used with permission.)

correct today, although in its initial form it tended to be qualitative, rather than quantitative. For example, although the need for vitamin D to promote active intestinal calcium absorption was recognized, the amount of vitamin D needed was not known.

#### REDUCING EXCESSIVE BONE REMODELING

The second mechanism of action has become apparent only very recently. Both calcium and vitamin D, particularly together, reduce excessive bone remodeling. Bone remodeling doubles across menopause and triples by the age of 65 y (11). Originally, remodeling had been envisioned primarily as a repair mechanism, replacing damaged bone with fresh new bone. Hence, remodeling was seen as osteoprotective. Although that function still remains important, the rise in remodeling after midlife appears to be driven by hormonal changes and nutritional factors rather than by the need to repair bone.

Several lines of evidence show that high remodeling rates increase bone fragility (12–16) and that the reduction in fragility that follows antiresorptive therapy is probably due more to the effect of the therapy on remodeling than to its effect on bone mass (13, 14). Moreover, remodeling suppression begins immediately on institution of either pharmacologic or nutritional antiresorptive interventions, and careful analysis of the fracture curves of several published studies shows that fracture risk reduction begins essentially immediately as well, before any appreciable effect on bone mass can be detected (16). This point is shown in **Figure 1** for 2 of the antifracture efficacy trials of calcium and vitamin D (17, 18). These studies, published more than a decade ago, were part of the basis for current calcium intake recommendations.

Both increased calcium intake and increased vitamin D status reduce bone remodeling because they reduce parathyroid hormone secretion. Calcium alone will do that via passive absorption if the intake is high enough (probably well in excess of 3000 mg/d); vitamin D acts by facilitating active calcium transport from more typical calcium intakes.

Remodeling is a contributor to fragility because bony trabeculae bend under weight-bearing loads, and if there is a resorption

bay in the side of a trabecula, the load is transferred to a much smaller cross-section. Bending of these compromised structures frequently produces trabecular microfractures. These fractures are clinically silent but are prevalent and contribute greatly to the fragility of skeletal structures containing an appreciable amount of cancellous bone subject to exaggerated remodeling. Thus, any agent that slows the rate of activation of new remodeling loci (bisphosphonates, estrogen, selective estrogen receptor modulators, calcium, vitamin D) produces a prompt reduction in bone fragility.

#### ANTIFRACTURE EFFICACY

Although antifracture efficacy has been well documented for calcium, the efficacy of vitamin D alone has been less well studied. Heikinheimo et al (19), nearly 15 y ago, reported a reduction in osteoporotic fractures in both home-living and institutionalized elderly with large, single, annual injections of vitamin D. The Finnish population concerned has a naturally high calcium intake but generally low vitamin D status; hence, vitamin D was likely the limiting nutrient.

More recently, Trivedi et al (20), in a 5-y randomized controlled trial of vitamin D supplementation (alone) in England, produced a 33% reduction in principal osteoporotic fractures in the vitamin D-treated arm. Two subsequent studies from the same national population, using the same average daily dose of vitamin D, showed no change in fracture risk (21, 22). There was, however, a crucial difference in execution of the 3 studies. In the study by Trivedi et al, vitamin D was given only 3 times per year (in doses of 100 000 units each), a regimen optimizing treatment adherence. In the other 2 studies, vitamin D was given as a daily oral dose. Serum 25(OH)D was elevated from  $\approx 50$  to  $\approx 74$  nmol/L in the study by Trivedi et al but did not achieve comparable levels in the other 2 studies, indicating a substantial difference in degree of compliance with the taking of study medication. In 1 of the 2 failed trials, documentable compliance was in the range of 40% (21), a value congruent with the small rise in 25(OH)D reported.



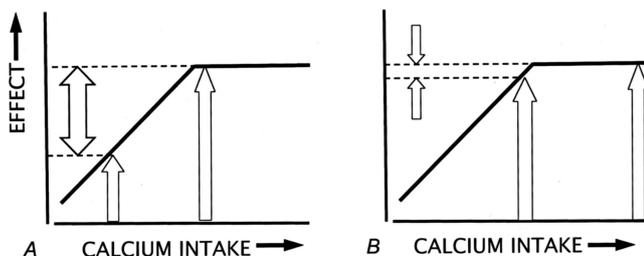
Whether the decline in fracture rate in the study by Trivedi et al was due to improvement in lower-extremity muscle function and fewer falls (23) or to better utilization of dietary calcium and reduced bone remodeling (or both) cannot be determined from the available data. In one sense, the distinction is perhaps less important: as noted at the outset, the 2 nutrients are needed together and, even where their actions are independent, they are nevertheless complementary. In any event, meta-analyses of various controlled trials of vitamin D, using both hip fracture and falls as outcome measures (24, 25), show that, for either outcome, there is a statistically significant improvement when all the trials concerned are aggregated.

Finally, there is a unique consideration relating to vitamin D that is often not given adequate attention. It is the serum 25(OH)D value that is important with respect to the various measured outcomes, and not the oral dose of vitamin D. Precisely for this reason, meta-analyses and systematic evidence reviews need to use as the input variable the serum 25(OH)D concentration achieved in a trial, not the oral dose used. In this respect, vitamin D is unlike nearly all other nutrients. Fully normal vitamin D status is possible with zero oral intake, simply because most of the vitamin D used by our bodies each day comes from cutaneous synthesis, and the quantities normally produced in this way far exceed the small intakes that are enshrined as the recommended intakes in the Dietary Reference Intakes (7). (The recommended intakes are adequate only to prevent the development of rickets or osteomalacia in individuals effectively deprived of solar exposure.)

### THE IMPORTANCE OF THE EFFECT THRESHOLD

With respect to the first mode of action (the offsetting of obligatory losses), calcium functions as a threshold nutrient, that is, calcium retention improves as calcium intake rises, up to some threshold intake value, above which no further increase in intake will alter retention. (In this respect, calcium is like iron which, in iron-deficiency anemia, results in an increase in hemoglobin but only up to physiologically normal values, above which further intake produces no further rise in hemoglobin.) This aspect of calcium's behavior is important for 2 reasons: 1) it is the criterion by which the calcium requirement for skeletal health needs to be judged, and 2) it has to be factored into the design and evaluation of studies to test the role of calcium when change in bone mass or calcium balance is used as the outcome measure.

Figure 2 displays schematically the threshold behavior of



**FIGURE 2.** Threshold curves for adults showing diagrammatically why, in studies testing the hypothesis that augmented calcium intakes will improve calcium retention (or its concomitants, bone mass and bone strength), one of the contrast groups must have an intake below the threshold value. (A) The ideal design. (B) The design used in several failed trials, notably the Women's Health Initiative (26). (Copyright Robert P Heaney, 2006. Used with permission.)

calcium and contrasts 2 design scenarios evaluating the skeletal effect of different calcium intakes. Scenario A would be predicted to show a difference in effect between the 2 calcium intakes, whereas scenario B would not. The calcium arm of the Women's Health Initiative (WHI) followed a pattern similar to that of scenario B (26). The WHI had no low-calcium-intake contrast group; those in the placebo arm had a calcium intake between 1100 and 1200 mg/d. The small increase in bone density and the nonsignificant reduction in hip fracture in the WHI (by intention-to-treat) can probably best be explained by the fact that, whereas the mean calcium intake going into the study was already at the threshold point, there would necessarily have been women with below-average intakes who would, therefore, have been able to respond to supplemental calcium.

Meta-analyses and systematic evidence reviews of published trials need to use the presence of a low-calcium-intake group as a criterion for inclusion in the analysis. Failure to do so loads the review with studies which no plausible hypothesis would have predicted might produce a measurable effect.

The second mechanism by which calcium is acting (the restoration of bone remodeling toward premenopausal normal values) probably also exhibits a threshold characteristic. However, it is not certain where its threshold point may be located. It must be to the right of the retention threshold intake and perhaps substantially so. Calcium intakes at or slightly above the threshold point, although they do not result in further calcium retention, are not yet high enough to restore remodeling to premenopausal values. In the sole study that looked specifically at that issue, an intake of 2400 mg/d was required to produce, in women in their mid-60s, average 24-h parathyroid concentrations and resorption biomarker excretion similar to those found in healthy premenopausal women (27).

Even calcium absorption, the canonical function of vitamin D, exhibits this threshold characteristic. The available evidence indicates that absorption efficiency is a linear function of increasing vitamin D status up to serum 25(OH)D concentrations of  $\approx 80$  nmol/L, above which higher inputs of vitamin D are without effect on absorption efficiency (28). In other words, vitamin D status is the limiting factor up to  $\approx 80$  nmol/L, above which other physiologic controls take over. In this context, values of serum 25(OH)D are serving simply as indicators of vitamin D status. Although it is likely that 25(OH)D exerts some absorptive effects in its own right, it is not necessary to postulate such activity in relating absorption efficiency to vitamin D status.

### VITAMIN D AND NEUROMUSCULAR FUNCTION

Vitamin D also improves lower-extremity neuromuscular function and reduces fall frequency (23, 24, 29–31), particularly in elderly individuals who are most prone to falling and fracture. In one study of elderly women with mean serum 25(OH)D values of 30 nmol/L, 800 IU vitamin D reduced falls by 49% within 12 wk of starting treatment (23). In a secondary analysis of data from a calcium–vitamin D intervention trial, vitamin D reduced falls by 56% in women generally and by 76% in sedentary women (29). Lower-extremity muscle function, measured in the National Health and Nutrition Examination Survey, showed continuing functional improvement as vitamin D status rose up to serum 25(OH)D values well in excess of 80 nmol/L (30), although the largest change occurred from 15 to 40 nmol/L. Similar measurements in the Amsterdam Longitudinal Aging Study also

showed substantial improvement in lower-extremity neuromuscular function as serum 25(OH)D rose (31). Finally, low serum 25(OH)D concentrations are a strong predictor of nursing home admission (32).

### VITAMIN D IN THE WOMEN'S HEALTH INITIATIVE

An illustration of the importance of the distinction between oral intake of vitamin D and serum 25(OH)D is provided, once again, by the calcium and vitamin D arm of the WHI, in this case with respect to the hypothesis that improved vitamin D status would reduce the risk of incident colon cancer. The vitamin D-treated arm did not exhibit a decrease in risk. However, baseline 25(OH)D status was significantly inversely correlated with risk. Those in the bottom quartile (<31 nmol/L) had 2.5 times the risk of those in the top quartile (33). There actually is no contradiction between these seemingly disparate findings in the same women, because the design dose of vitamin D in the WHI was 400 IU/d (and the achieved dose probably only one-half that). By contrast, it can easily be calculated that the dose required to move individuals from the bottom quartile to the top quartile is on the order of 2000 IU/d, or effectively 10 times what the individuals concerned actually received (34). 

The author had no conflicts of interest.

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