



Calcium and vitamin D

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Calcium and vitamin D constitute the foundation of any preventive or therapeutic regimen for osteoporosis. This is because bone is 50% mineral by volume and because maintenance or augmentation of bone mass requires an intake sufficient to offset daily calcium losses and to support bone gain. The only real questions are “how much?” and “why so much?”

The primitive inputs of calcium and vitamin D, to which human physiology is adapted, would have been high by contemporary standards. It is estimated that stone-age human hunter-gatherers had diets with calcium nutrient densities of about 2 to 2.5 mmol/100 kCal [1] or, for individuals of contemporary body size doing the work of a forager, total daily intakes of 60 to 75 mmol. At the same time, early hominids, evolving in equatorial East Africa, would have had cutaneous vitamin D synthesis sufficient to support serum 25(OH)D levels of approximately 150 nmol/L [2]. By contrast, contemporary sedentary North American and European individuals have calcium intakes of approximately 15 mmol/d and, even with fair skins, serum 25(OH)D levels generally below 80 nmol/L. Dark-skinned individuals in temperate latitudes have 25(OH)D levels lower still—generally averaging below 50 nmol/L. Prevailing contemporary inputs of both nutrients stress even a healthy organism and limit or preclude therapeutic response in the treatment of osteoporosis.

Calcium

Human physiology is adapted to the high calcium diet that prevailed during primate and hominid evolution. This is evidenced in the fact that at primitive calcium intakes, net calcium absorption (defined as the difference between oral intake and fecal output) in adults averages only 10% to 11%,

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renal calcium conservation is weak, and dermal losses are unregulated. Thus, for a 25-mmol intake, net calcium absorption is only about 2.5 mmol, half of which is spilled into the urine during the very slight absorptive calcemia that follows calcium ingestion. That leaves 5% of the intake (1.25 mmol) to offset obligatory skin and renal losses or to support bone gain. Under sedentary conditions, cutaneous losses alone are estimated to be on the order of 0.4 to 1.4 mmol/d [3], and, with exercise and sweating, such losses can rise to above 7 mmol/d, a drain great enough to produce a measurable change in bone mass across an athletic playing season [4]. Hence, an intake of 25 mmol/d may be insufficient for skeletal maintenance, let alone for support of anti-osteoporosis therapy.

Calcium conservation, weak at best, is nevertheless dependent upon estrogen status. Intestinal absorption and renal tubular reabsorption of calcium decline after menopause and can be returned to premenopausal levels by estrogen replacement therapy (ERT) [5–7]. It also seems that the more gradual worsening of calcium conservation that occurs in aging men is due to a decline in endogenous estrogen levels [7–9]. Whatever the mechanism, the age-related change in calcium conservation in both sexes is the ultimate reason for the rise in calcium intake recommendations after age 50 [10].

Vitamin D

Vitamin D is an uncertain nutrient: It is not a normal constituent of most foods but is typically produced endogenously by a cutaneous photosynthetic reaction, in which solar UV radiation converts 7-dehydrocholesterol into pre-vitamin D₃ (which then rapidly isomerizes in the skin to cholecalciferol [vitamin D₃]). Nutrient or not, vitamin D is essential for optimal physiologic functioning. Cholecalciferol is stored bound to D-binding protein, is slowly converted to 25(OH)D₃ in the liver, and is then hydroxylated at the 1- α position in the kidney to 1,25(OH)₂D₃ (calcitriol). Calcitriol functions as a hormone, influencing calcium absorption by binding to a mucosal nuclear receptor and inducing the synthesis of a calcium-binding transport protein needed for active calcium absorption across the intestinal mucosal barrier. Calcitriol's synthesis in the kidney is stimulated by parathyroid hormone (PTH) and by low serum inorganic phosphate concentration.

In the absence of calcitriol, intestinal absorption is solely by the passive, extracellular route, which limits gross absorption to about 12.5% of intake. Because digestive secretions and shed mucosa introduce about 3.5 to 4 mmol ca /d into the intestinal stream (ie, a flux in the opposite direction), it follows that even a calcium intake as high as 25 mmol/d is insufficient to prevent the gut from serving as a route of loss for calcium in the absence of calcitriol. (Net absorption in this example would be given by $(0.125 \times 25) - 3.75$, or -0.625 mmol; ie, 0.625 mmol more is coming out in the feces than is going in at the mouth.)

The relationship between unidirectional absorption and net absorption is depicted in Fig. 1, which shows, for various levels of active absorption, the calcium intakes required to put the gut into positive balance of any given magnitude. In the absence of active absorption, an intake of ~26 mmol is required to prevent net intestinal loss, and an intake of >60 mmol is required to offset cutaneous and renal losses, totaling 5 mmol/d. Without active absorption, no bone gain at all would be possible below this intake.

Although calcitriol is considered the hormonally active form of the vitamin responsible for regulating active calcium transport, it seems that 25(OH)D concentration also plays a role [11]. Before the discovery of calcitriol, 25(OH)D was used effectively in the treatment of renal osteodystrophy [12], and several recent studies have shown better correlation between serum 25(OH)D levels and calcium absorption efficiency than between serum calcitriol and calcium absorption [13,14]. This may be explained by a phenomenon termed transcaltachia [15], in which 25(OH)D binds to a mucosal receptor and augments transcellular calcium transport in cells in which calcitriol itself has induced synthesis of the calcium-binding

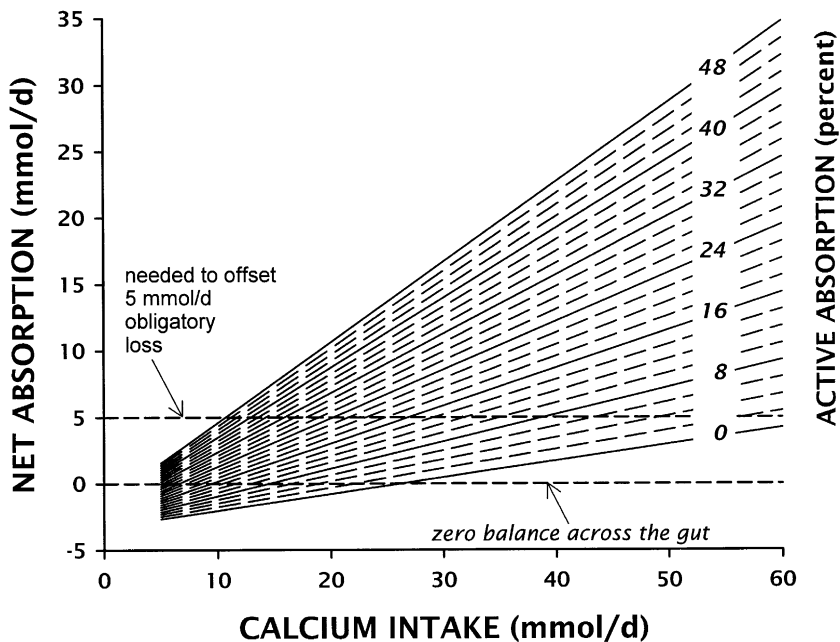


Fig. 1. Relationship between calcium intake and net absorption for varying levels of active absorption (indicated at the right of the contour lines). Net absorption is defined as the difference between oral intake and fecal output. The various contour lines are plots of the equation: $NetAbs = (Intake + 3.75) \times (PassAbs + ActAbs) - 3.75$, where $PassAbs$ = passive absorption fraction (≈ 0.125), and $ActAbs$ = active absorption fraction. (Copyright Robert P. Heaney, MD, 1999; with permission.)

protein. Hence, calcium absorption efficiency at a whole organism level is probably best explained by a combination of calcitriol and 25(OH)D effects, and absorptive regulation is optimal when serum 25(OH)D concentration is relatively high.

The vitamin D requirement, defined as the quantity the body must make or ingest each day to optimize D-related functions, is uncertain. Traditional oral intake recommendations (eg, 400 IU or 10 µg/d) were pegged to the amount required to prevent the expression of clinical rickets [16], but such recommendations ignore cutaneous inputs and the need to ensure extra-skeletal functions of the vitamin. There is limited but strong evidence that daily vitamin D inputs from all sources are in the range of 3000 to 5000 IU (75 to 125 µg) in healthy adults [2,17]. Given prevailing *oral* intakes, it follows that most of this daily use is met by vitamin D that has a cutaneous origin. Although such an input may be taken for granted in healthy adults, it must not be ignored in older individuals who have both reduced sun exposure and reduced efficiency of photoconversion of 7-dehydrocholesterol to vitamin D₃ [18].

There is no general consensus on normal values for serum 25(OH)D. Nominal laboratory reference ranges usually place the lower limit at 40 to 50 nmol/L, but there is a growing body of evidence indicating that levels below 80 nmol/L impair optimal functioning of several systems and therefore should not be considered normal. For example, PTH levels rise as serum 25(OH)D levels fall below 80 nmol/L but are unchanged above 80 nmol/L [19,20]. Although this secretion of PTH has been characterized as a normal physiologic response to an inadequate calcium intake (and hence not an indication of insufficiency) [21], increased secretion of epinephrine and cortisol under conditions of stress are also normal physiologic responses. However, that fact does not mean that it would be healthful to live with such high levels continuously. Elevated PTH raises bone remodeling, which is now recognized to be associated with increased fracture risk [22]. Moreover, recent evidence indicates that calcium absorption efficiency rises substantially as 25(OH)D levels increase from 50 to 80 nmol/L [23], whereas calcium absorption is unchanged on further increases of 25(OH)D [24].

Hence, at the existing state of our understanding, it seems prudent to consider 80 nmol/L as the lower limit of normal and to provide our patients with sufficient oral D to achieve and sustain such a level. For most patients with osteoporosis, this means an oral intake of at least 1000 IU/d (25 µg/d).

Prevention

A very large body of studies, summarized in detail elsewhere [25], demonstrates that augmented calcium intakes increase bone acquisition during growth, slow age-related bone loss, and reduce fragility fractures in the elderly population. Moreover, there is general agreement that a high

peak bone mass is strong protection against low bone mass and its associated fragility late in life [26]. During adolescent growth, almost 40% of adult bone mass is potentially accrued [27]. A number of environmental factors influence achieving maximal peak bone mass within the genetic potential; these include diet, exercise, and other behaviors such as tobacco and alcohol use and eating disorders [26,28]. Increasing calcium/dairy food intakes has enormous potential for increasing peak bone mass. The mean calcium intake for adolescent girls age 9 to 13 years in the United States is 23 ± 1 mmol/d, compared with the intake required for mean maximal calcium retention of 32.5 mmol/d [10,29].

One of us (CMW) has studied calcium retention on a range of calcium intakes in adolescent girls [30]. Using the nonlinear regression equation developed from this relationship, increasing calcium intakes from the average intake of 23 mmol/d to 32.5 mmol/d increases net calcium retention by 2.8 mmol/d (Fig. 2). If this much extra calcium were retained for 1 year, an additional 4% of skeletal mass could be accrued. Thus, the average American girl during the time of maximum bone accrual is gaining bone at only two thirds of her potential. The temporal window of opportunity for achieving these gains is quite narrow. The average age for peak bone mineral content velocity in girls is at 12.5 years and at a rate of 8 mmol/d, whereas in

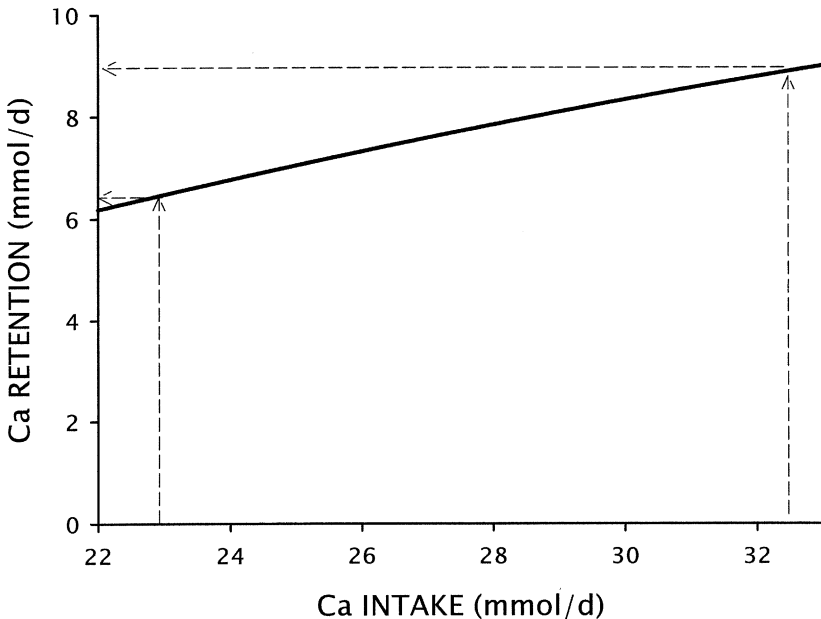


Fig. 2. Calcium retention as a function of intake in adolescent girls from the study of Jackman et al [30]. The daily increase in calcium retention when calcium intake is increased from the average intake of 23 mmol/d to recommended levels of 32.5 mmol/d is 2.8 mmol/d.

boys it is at 14 years at a rate of 10 mmol/d [31]. Much of bone accrual during adolescence occurs within a 2-year period. At 1 year on either side of the age of peak bone accrual, the rate of bone gain falls by approximately 40% of the peak velocity. An increase in bone mass during adolescence not only sets the stage for greater protection against fragility fractures later in life but is protective against fractures even while young [32].

Several of the more dramatic intervention studies in older populations used both calcium and vitamin D [33,34], a combination that seems essential in older individuals because both nutrients tend to be deficient after mid-life. Fig. 1 shows why this is so: Little benefit accrues from a supplemental calcium intake of as much as 25 mmol in the absence of vitamin D (ie, the bottom line in the graph). At a basal intake of 15 mmol/d (roughly the median intake in over-50 women in NHANES-III) [29], net absorption is negative (approximately -1.5 mmol/d), and although improvement does occur with the extra 25 mmol of calcium, net absorption at 40 mmol/d is still less than the amount needed to offset urinary and skin losses. Hence, no perceptible *bone* benefit could occur with such a supplement in the absence of vitamin D-mediated active absorption.

The relative importance of calcium and vitamin D was shown in a study by Peacock et al [35] in which elderly individuals were randomized to receive 19 mmol calcium, 15 μ g vitamin D, or placebo. Basal calcium intakes averaged 15 mmol/d, which, with the supplement, were elevated to a total of ~ 34 mmol/d. The placebo group lost bone mass at the total hip at a rate of 0.5% per year, whereas the calcium-supplemented group had an effectively stable bone mass for the 4 years of the trial. Vitamin D alone produced a result intermediate between placebo and calcium alone, with a loss averaging about 0.4% per year. However, basal 25(OH)D levels averaged 65 mmol/L (± 25), which is a value above the nominal reference limit, although probably not fully optimal. Adding extra vitamin D in individuals with severe calcium deficiency was not as effective at bone-sparing as was repleting only calcium in individuals with marginally adequate vitamin D status.

Many factors influence bone mass, and calcium nutriture is only one of them. A high calcium intake is not a substitute for exercise, hormonal adequacy, and good general nutrition, nor does it offset the negative skeletal effects of anorexia, estrogen deficiency, smoking, glucocorticoids, Graves' disease, or immobilization. The sole role of calcium in the adult insofar as bone is concerned is to replace the excretory and cutaneous losses that occur every day and that would otherwise have to be offset from skeletal reserves.

The average quantity necessary to offset such daily losses is approximately 25 mmol/d for adults to mid-life and 37.5 mmol thereafter. Three NIH Consensus Development Conferences (1984, 1994, 2000) have recommended such intakes [36–38]. The 1997 recommendations of the Food and Nutrition Board [10], when converted to RDAs, are essentially identical (the Food and Nutrition Board published recommendations

termed “Adequate Intakes – AIs” [10], which are numerically equal to average requirements; to make allowance for the needs of 95% of the population, these values need to be raised by 20% to 25%). These intake recommendations have thus been stable for nearly 20 years and would seem to be approximately adequate for bone health. It must be shared, however, that such intakes are designed to *maintain* the skeleton, and it is unlikely that the same intakes would be optimal for the support of a treatment-induced skeletal augmentation (see also below).

The status of the vitamin D recommendation is much less certain. If recent studies [2,17] are confirmed, it would seem that as much as 85% of usual daily vitamin D input in typical healthy adults is from the skin. This input in turn depends upon latitude, skin exposure, pigmentation, use of sun blockers, and age-related decline in cutaneous accumulation of 7-dehydrocholesterol. Because cutaneous vitamin D synthesis tends to decline with age, more reliance in the elderly population must be placed on oral sources (mainly milk and nutritional supplements). The age-related decline in cutaneous vitamin D input is the reason that the Food and Nutrition Board, in its 1997 recommendations, increased the recommended oral intake of vitamin D for older adults from the 1989 level [16] of 5 µg/d to 15 µg/d [10]. This three-fold increase is arguably the largest change ever made by the Institute of Medicine for a nutrient intake recommendation. It reflected the growing realization that absence of rickets/osteomalacia was not a criterion of vitamin D sufficiency. Even this higher value is inadequate for many older individuals, and it will be necessary in some cases to try varying intakes and to monitor serum 25(OH)D until an intake supporting the desired 25(OH)D concentration is found. In the central United States (40°–42° N latitude), it takes an average of about 25 µg/d to maintain a 25(OH)D level of 80 nmol/L in ambulatory older women. The needed quantity may be different in other groups.

Therapeutic support

The development and deployment of potent bone-active agents for the treatment of osteoporosis raises a question about the mineral intake that is optimal for support of the ability of such agents to add bone to the skeleton. Such bony augmentation requires an absorbed calcium intake greater than the sum of urinary and skin losses, and it is likely that recommended *maintenance* intakes may not be fully adequate for this purpose. Although it is evident that calcium is consumed in bone building, vitamin D is not, and so far as is known, the vitamin D requirement for therapeutic support is no different from that for maintenance. Hence, the remainder of our discussion under this heading relates mainly to calcium. All of the approved agents for treatment of osteoporosis have been tested in the presence of added calcium (500–1000 mg/d) and in some cases added vitamin D as well (but generally

up to no more than 10 $\mu\text{g}/\text{d}$, and usually less). It can confidently be said that we do not know what the efficacy of these agents is without calcium. Nor do we know whether the amount of calcium used was sufficient to allow the various treatment agents to exert their full effects.

The importance of using calcium along with bone active agents was first suggested by observational data from the Hawaii Osteoporosis project [39], in which postmenopausal women given ERT alone exhibited the expected bone-sparing effect, whereas calcium alone had only a very small effect that was of marginal significance. The combination of the two agents had a substantially greater bone-sparing effect than ERT given alone. Then, in a meta-analysis of 31 published trials of ERT, Nieves et al [40] showed (Fig. 3) the same augmentation of ERT's effect by added calcium. The authors contrasted 10 studies that did not use supplemental calcium (mean calcium intake <15 mmol) with 21 studies that had used supplemental calcium (mean calcium intake ~ 30 mmol). As in the Hawaii study, bone gain with the combination of calcium and ERT was greater at all measured sites, by a factor of $2\times$ to $4\times$. Recker et al [41], in a randomized, controlled trial, showed that ERT in a dose of 0.3 mg of conjugated equine estrogen (a dose previously thought to be ineffective) produced an $\sim 5\%$ augmentation of lumbar spine bone mineral density in women given sufficient calcium to raise intakes in all of them above 25 mmol/d and sufficient vitamin D to produce serum 25(OH)D levels above 75 nmol/L. Finally, Honkanen et al

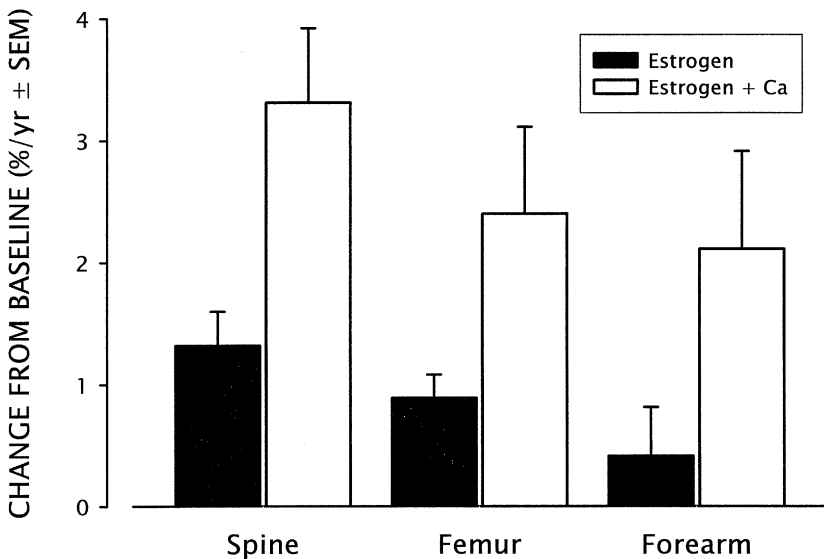


Fig. 3. Bone mass response to estrogen replacement in postmenopausal women, with and without supplemental calcium. Redrawn from the data of Nieves et al [40]. (Copyright Robert P. Heaney, MD, 1998; with permission.)

[42], in a population-based, epidemiologic study from central Finland, showed that, whereas ERT alone or a high calcium intake alone reduced risk of Colles fracture by 30%, the combination of the two reduced the risk by 70% (Fig. 4).

All trials of bisphosphonates and raloxifene have used supplemental calcium and, in some instances, small amounts of vitamin D. However, with no untreated control group and no systematic variation in the calcium and vitamin D inputs, it is not possible to know with certainty how much the calcium contributed to the bone gain reported for these agents. Remodeling suppressors typically produce a remodeling transient that at the spine results in a ~4% to 5% gain in bone mineral and then a steady-state continuing bone gain at a rate of 0.5% to 1.0% year [43]. Both of these gains mean that absorbed input of calcium must be greater than excretion. This is not possible without adequate oral intake. However, some of the bone gain with anti-resorptives comes about because the remodeling suppressors reduce bony response to PTH, forcing higher endogenous PTH secretion and better conservation of whatever calcium may be in the diet [43]. Nevertheless, it is unclear whether bone gains reported with remodeling suppressive treatments are as high as possible because no trial has been conducted with calcium intakes above (or in some cases *even as high as*) the currently recommended *maintenance* intake. Nor has any trial of anti-resorptive

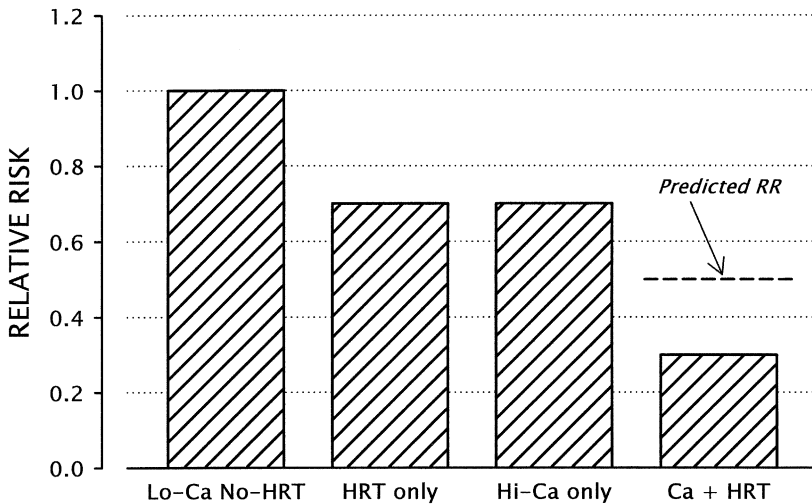


Fig. 4. Relative risk of sustaining a Colles fracture for women in central Finland, as a function of estrogen replacement and level of calcium intake [42]. A relative risk of 1.0 was assigned to those declining estrogen and choosing diets with low calcium content. Constructive interaction between estrogen and calcium is indicated by the greater reduction in risk for the combination than would have been predicted if their effects were independent. (Copyright Robert P. Heaney, MD, 2002; with permission.)

agents ensured a vitamin D intake sufficient to elevate 25(OH)D to 75 to 80 nmol/L or above in all subjects.

Recombinant human PTH (rhPTH, teriparatide) constitutes a near quantum leap in bone-building potency, with reported gains in lumbar spine bone mineral density ranging from 9% to 15% per year [44,45]. Even if calcium intake were not limiting with anti-resorptive agents, it is likely that it would be with an agent such as teriparatide. Such bone gain is the largest a woman would have experienced since her adolescent growth spurt. In the trial by Neer et al [45], bone gain at the spine occurred at a rate of ~10% per year, using calcium at a dose of 25 mmol/d and vitamin D at doses of 10 to 30 µg/d. The smaller trial by Arnaud et al [44] produced a bone gain of ~30% by 2 years at the lumbar spine and approximately 12% at the hip. Arnaud et al used 50% more calcium (37.5 mmol) than Neer et al, and the greater bone gain they found suggests that effective mineral intake in the Neer trial may have limited therapeutic response.

Until dose-response studies establish the no-effect level for calcium during treatment of osteoporosis with any currently approved agent, it is prudent to use at least 37.5 mmol/d and to ensure a serum 25(OH)D level of 80 nmol/L or higher.

Sources

Calcium

The best source of calcium is food, principally dairy products or fortified foods that have established the bioavailability of their added calcium. The reason for the preference for food is that bone health is not a mononutrient issue. High intake of protein [46,47], potassium [48], magnesium [48], and phosphorus [49] contribute to bone health directly or augment the effect of their calcium content. Dairy foods, particularly milk and yogurt, are the best and most economical way to get all of these nutrients in a single package.

Some dependence upon calcium supplements is usually necessary, however. Here, despite manufacturers' claims to the contrary, all chemical salts of calcium are about equivalently absorbed [50–52], and choice among the various competing brands should be based on convenience, cost, and tolerability. One should find a source that optimizes long-term adherence. Although the different chemical salts are absorbed similarly, different pharmaceutical formulations, even of the same salt, may not be. Carr and Shangraw [53] showed this clearly in *in vitro* studies several years ago, leading to adoption of disintegration and dissolution standards by the USP for calcium supplements. However, manufacturer compliance with these standards is voluntary. Moreover, disintegration and dissolution, *in vitro*, do not correlate well with *in vivo* bioavailability [54], and unpublished data from the laboratory of one of us (RPH) indicate that some formulations in

use exhibit substantially reduced absorbability. Hence, it may be safest to rely principally on the few marketed products that have established (and published) absorbability data.

Although it is probably not a major factor for bone maintenance or support of anti-resorptive therapy, phosphorus intake may become rate-limiting with agents such as teriparatide. A small, but not negligible, fraction of older women ingest less than 70% of the RDA for phosphorus on any given day [29], and high-dose calcium supplements (if given as the carbonate or citrate salts, for example) bind most or all of the phosphorus of such diets in the intestine, preventing its absorption [49]. Bone mineral consists of calcium *and* phosphorus (as an imperfect hydroxyapatite), and net mineral addition manifestly requires *both* minerals. Hence, for patients treated with teriparatide and with limited meat and dairy intakes, the preferable calcium salt is probably a calcium phosphate preparation.

Vitamin D

Although there is an abundance of calcium supplements available in the US market, there is a distinct shortage of good vitamin D preparations. Many calcium supplements contain added vitamin D, usually in amounts approximating 0.4 $\mu\text{g D/mmol Ca}$. Similarly, milk contains vitamin D at a level of 0.33 $\mu\text{g D/mmol Ca}$. Neither level of fortification is sufficient to provide an intake of vitamin D as high as recommended above, even if calcium from these combined sources reaches the recommended 37.5 mmol/d. A single multivitamin supplement usually contains 10 μg of vitamin D, so one such capsule each day, together with milk and use of calcium supplements containing vitamin D, may be sufficient to achieve desired 25(OH)D levels in most patients. This presumes substantial solar input through cutaneous vitamin D synthesis. When this cutaneous input is low, supplemental vitamin D monotherapy is required. Pharmacies do not regularly stock vitamin D-only preparations but often do so if physicians specifically request that they be made available to their patients. Ergocalciferol (vitamin D₂) is available as a prescription preparation in a 50,000-IU formulation, and in some situations this dosage form may be suitable. However, vitamin D₂ has substantially less potency than vitamin D₃ (cholecalciferol), so the amount of ergocalciferol required to achieve a given 25(OH)D level may be as much as twice the dose required if cholecalciferol had been used [2].

The quickest and safest way to achieve desired 25(OH)D levels is to supply 25(OH)D₃ itself in a pharmacologic preparation. A dose averaging 10 $\mu\text{g/d}$ suffices for most purposes. Unfortunately, the sole pharmaceutical supplier of this product in the United States has stopped production, and it is unclear if or when this otherwise quite good product will become available once again to US physicians.

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