

Role and Importance of Calcium in Preventing and Managing Osteoporosis

Introduction

Recent publication of studies evaluating the effects of calcium on bone health has raised questions about the role and importance of calcium in preventing and treating osteoporosis.^[1-3] Therefore, it may be timely both to review this issue once again and attempt to understand why study results may sometimes be discordant.

To begin with, it is important to recall that there is a huge body of evidence supporting the importance of an adequate calcium intake throughout life. This evidence is summarized exhaustively in the reports of 3 National Institutes of Health (NIH) Consensus Development Conferences,^[4-6] in the calcium chapter of the Dietary Reference Intakes for Calcium and Related Nutrients,^[7] in the scientific background document for the Dietary Guidelines for Americans,^[8] and in the recent Surgeon General's Report on Bone Health and Osteoporosis.^[9] The conclusions, promulgated by the various government agencies concerned, are that calcium intake should be in the range of 1000 mg/d up to age 50 years, and from 1200-1500 mg/d thereafter. The NIH, sponsors of the Women's Health Initiative (WHI) trial of calcium and bone health, have stated publicly that nothing in recent publications of WHI data changes those recommendations.^[10]

The median calcium intake in postmenopausal women in North America is about 550-650 mg/d,^[11] substantially below existing recommendations. This raises 2 important questions related to bone health: (1) Is prevailing calcium intake inadequate? (2) Would raising prevailing intake by about a factor of 2 (to currently recommended levels) confer a skeletal benefit (ie, result in fewer fractures)? When these questions were addressed in properly conducted randomized trials, the answer was clearly "yes" to both.^[12-15] Bone mass is conserved, and fractures are reduced by 45% to 55%.

PE 06

Nutritional Background

Two thirds of bone mass is mineral -- principally calcium phosphate -- and a healthy adult human body contains 1000-1400 g of calcium, 99% of which is found in the bones and teeth. At birth, an infant's body typically contains 25 to 30 grams of calcium, and the roughly 1000-g difference must come into the body by way of the diet. This much is virtually self-evident. All nutrient intake recommendations for laboratory animals and pets, as well as nonhuman primates, are high in calcium, for purposes of both growth and maintenance.

Humans are at the low end of the calcium intake spectrum. When expressed per unit of energy in the diet, animal calcium intake recommendations are from 3 to 10 times higher than current recommendations for humans.

Calcium serves 2 major functions for bone. First, it is the bulk cation from which bone mineral is constructed. As such, it must be absorbed in sufficient quantity from

ingested foods to build a skeleton during growth and to maintain skeletal mass in maturity (the latter by offsetting obligatory losses from the body). Second, it serves as an indirect regulator of skeletal remodeling. The first function has dominated the attention of the clinical nutrition community through most of the past century and provides the foundation for the impressive array of calcium nutritional policy statements referenced above. The second is only now emerging as an important contributor to bone strength.

Calcium as a Source and Sustainer of Bone Mass

There are 2 main physiologic reasons why calcium intake needs to be high: poor absorption and weak conservation. Through most of life, net absorption efficiency for calcium averages only about 10% of intake. The sole exceptions are during infancy, a brief period at the adolescent growth spurt, and during the latter half of pregnancy. Daily obligatory losses through urine and skin average about 200 mg/d in sedentary adults^[16] and can be substantially larger under conditions of strenuous exercise.^[17] Bone functions as the body's calcium nutrient reserve, and when obligatory losses exceed absorbed intake, bone is destroyed to scavenge its calcium. Unlike sodium, which can be tightly conserved in an acclimated, trained individual, calcium conservation is always poor, probably because of calcium abundance in the foods consumed by evolving hominids. Available evidence indicates that calcium intake of preagricultural humans was substantially higher than were those following the agricultural revolution.^[18]

The literature documenting the protective effect of calcium is summarized in the various consensus documents and policy statements cited earlier.^[4-9] In brief, augmenting calcium intake above prevailing levels increases bone gain during growth, reduces bone loss after midlife, and reduces fragility fractures. At last count, there were in excess of 100 metabolic/physiologic and randomized, controlled trials, more than 90% of which demonstrated the previously cited benefits. In addition, there have been over 145 observational studies, about 80% of which have also been positive. Thus, there can be no serious doubt about the importance of adequate calcium intake, both to amass the adult skeleton programmed into our genome and to maintain skeletal mass in light of ongoing daily obligatory losses. The question is not whether calcium is important, but rather, how much is enough?

Calcium as a Regulator of Remodeling

Recent work strongly suggests that calcium produces beneficial effects not only through protection of bone mass but through regulation of bone remodeling. The term "remodeling" refers to removal and replacement of small volumes of bone, a process that continues throughout life. Broadly speaking, remodeling of bone serves 2 closely linked purposes: (1) repair of fatigue damage and the reshaping of bone to accommodate growth and altered usage; and (2) as a source and sink for calcium in the protection of extracellular fluid (ECF) [Ca²⁺].

In the reconstructive phase of remodeling, bone mineralization takes calcium and phosphorus out of the circulating blood, creating a mineral deficit in the ECF that constitutes the principal systemic stimulus for parathyroid hormone (PTH) secretion. PTH, in turn, is the principal determinant of the quantity of bone resorption occurring throughout the skeleton. In this sense, bone mineralization "pulls" bone resorption. In parathyroidectomized animals and in humans with hypoparathyroidism, total bone remodeling drops to levels less than one sixth the value found in intact organisms. The result, however, is usually hypocalcemia.

During periods of fasting or low calcium intake, PTH secretion rises, and with it, bone resorption (and, thereby, total bone remodeling). From a homeostatic perspective, such remodeling contributes the calcium needed to maintain ECF $[Ca^{2+}]$. However, structurally, homeostatic remodeling contributes only weakness, because bone at sites being remodeled is locally reduced in mass and, hence, in strength.

This strength reduction is illustrated in Figure 1, which shows that a resorption cavity in the side of a load-bearing bone trabecula produces local weakness out of proportion to the modest reduction in mass.

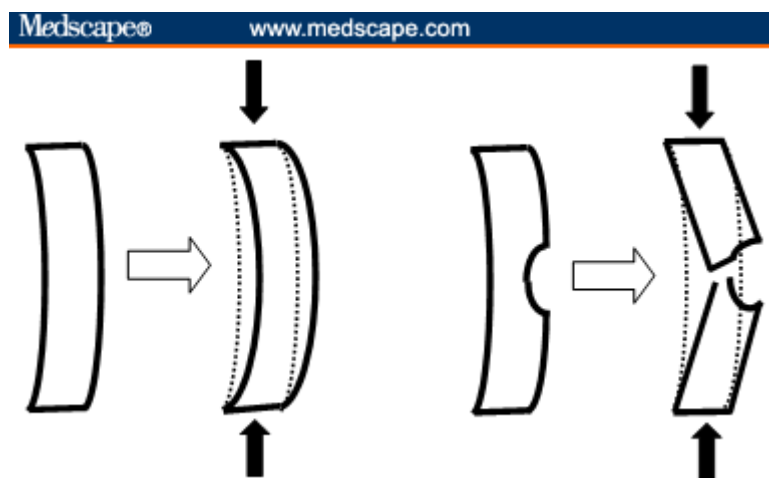


Figure 1. Strength reduction.

Diagram showing that vertical trabeculae bow slightly when loaded. Resorption pits in the side of such trabeculae serve as stress concentrators, since the prior load must now be borne by a smaller cross-section. The result is a tendency to snap with usual load-bearing activities. Hundreds of such healed or healing trabecular fractures can be found in osteoporotic bone by microdissection. (Copyright Robert P. Heaney, 2005. Published with permission.)

Over the short term, this loss in strength is trivial, but if inadequate calcium intake is continuous, then remodeling and fragility remain high. The number of these compromised trabeculae accumulates and bone mass ultimately declines measurably as well. It is important to note, however, that the increase in fragility precedes appreciable loss of mass, and is due, as Figure 1 illustrates, to compromised structures.

Until recently, clinical bone biology has focused primarily on the ultimate effect of calcium intake on bone mass. This emphasis explains why calcium balance, or change in bone mineral density (BMD), has been the primary outcome variable in many studies of nutritional or pharmacologic interventions. Virtually all such studies show that increasing calcium intake to or above age-specific thresholds leads to greater bone gain in young people and to decreased age-related bone loss in the elderly.^[4-9, 16]

But the matter is more complex than that. When an intervention that reduces remodeling is first started, bone resorption slows immediately -- as soon as PTH levels drop. Ultimately, bone mass may change as well, but it now seems likely that simply reducing remodeling is substantially more important than the mass change -- at least over the short term, when the remodeling change is fully expressed but the mass change is just beginning.

This conclusion first became apparent in the analysis of osteoporosis treatment trials, in which BMD change was found to explain less than half of the fracture reduction at the end of the trial.^[19] More striking still are the results from a secondary analysis of outcomes from the fracture intervention trial.^[20] Reduction in fracture risk was separately assessed for those who had improved BMD under treatment and for those who did not. Fracture risk was reduced to the same extent for both groups, strongly suggesting that BMD change was of little importance and that it was the remodeling reduction that was responsible for reduced fracture risk.

Like the bisphosphonates, calcium functions as an antiresorptive agent, although its mechanism of action is different. Calcium reduces remodeling by directly reducing PTH secretion. For example, McKane and colleagues^[21] showed that high calcium intake (about 2400 mg/d) in healthy postmenopausal women reduced 24-hr PTH levels by 40%. Using short-duration calcium kinetic studies in children, Wastney and colleagues^[22] showed that increases in calcium intake suppress bone resorption without affecting bone formation, at least over the life of 1 remodeling cycle. The role of remodeling adjustment in support of calcium homeostasis was strikingly exemplified by their data, as increased absorption from food was matched, milligram for milligram, by decreased calcium release from bone through reduced bony resorption.

Even more to the point, fracture reduction begins immediately after treatment is started, before an appreciable mass difference can develop.^[23,24] Analysis of the fracture risk curves reported for 2 major calcium and vitamin D intervention studies^[12,13] clearly showed that reduction in fracture risk occurs almost immediately. Figure 2 is a replot of some of the fracture data from these trials, showing unequivocally that supplemental calcium and vitamin D promptly reduce fracture risk.

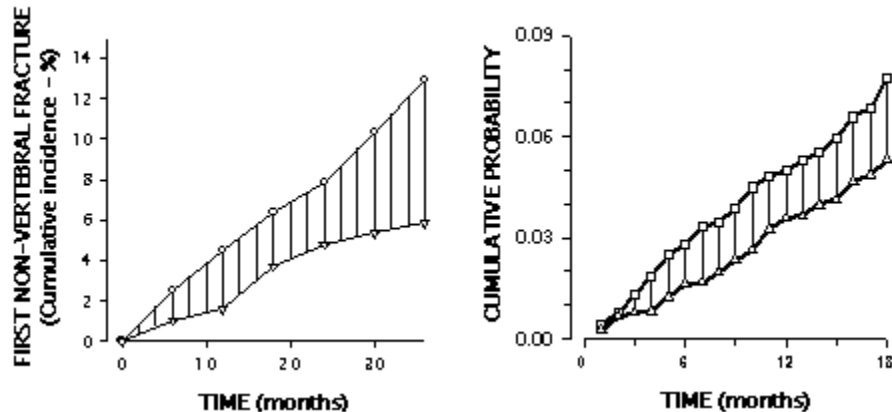


Figure 2. Fracture risk reduction.

Plots of the cumulative incidence of fractures, redrawn from the studies of Chapuy and colleagues^[12] (right) and Dawson-Hughes and colleagues^[13] (left). In both cases, the upper line represents the placebo control group and the lower line represents participants treated with calcium and vitamin D. The shaded zones represent the reduction of fracture risk, which, as can be readily seen, starts at the beginning of treatment. (Copyright Robert P. Heaney, 2004. Published with permission.)

Both increased mass and reduced remodeling during calcium augmentation are now understood to increase bony strength. What the remodeling effect means is that, with adequate calcium intake, individuals with substantial bony deficits have a prompt reduction in fragility, without having to wait for the mass deficit to be fully repaired -- something that is often not feasible, at least not by nutritional means alone. Further, the benefit consists of an absolute reduction in fracture risk, not simply a slowing of the progressive fragility of aging that had originally been judged to be the goal of stopping age-related bone loss.

In truth, both effects occur. For example, in the study by Chapuy and colleagues,^[12] bone loss, which amounted to greater than 3%/yr at the hip in control group participants, stopped entirely in the participants supplemented with calcium and vitamin D. At the same time, as Figure 2 shows, fracture rate decreased well before change in bone mass could be expressed.

These observations have raised such questions as whether suppressing remodeling is a good thing and what the optimal rate of bone remodeling is. In mature adults, bone turns over at an estimated rate of 8% to 12% per year. However, cancellous bone regions that are in contact with red marrow are replaced at 2 to 3 times the average rate and the cortical bone of long bone shafts at about half this rate or less.

Remodeling is known to repair fatigue damage and, hence, has generally been considered to be a positive factor for bone strength overall. Moreover, the magnitude of remodeling has been assumed to be driven mainly by this need for structural repair. Thus, reduced remodeling, to the extent that fatigue damage is allowed to accumulate, had been predicted to increase bony fragility. For this reason, it came as

a surprise when reduced remodeling was found to be the probable reason for reduced fracture risk shown in the osteoporosis treatment trials.^[19,20]

The explanation now considered most likely is that most remodeling is homeostatic rather than structural.^[25] Homeostatic remodeling, though contributing calcium, decreases bone strength focally. In addition, recent research quantifying remodeling has shown that cancellous bone remodeling increases 2-fold across menopause and is about 3 times the premenopausal level by the mid-60s.^[26] This change, almost certainly not driven by mechanical need, is the likely cause of the greatly increased bone fragility in postmenopausal women.

The premenopausal rate, measured histomorphometrically, is about 6% to 7%/yr at the iliac crest. In contrast, Parfitt^[27] recently estimated that a remodeling rate of 2%/yr should be sufficient to repair fatigue damage. Whatever the optimal structural rate may be, it now seems certain that there is a relatively large excess of remodeling in ostensibly healthy, adult humans in developed countries, which has its basis not in structural repair but in calcium homeostasis. To the extent that such remodeling is a source of weakness, it follows that remodeling reduction will strengthen bone -- which is what the data have shown.

What Causes High Levels of Remodeling?

The reasons for what is now recognized as a high level of homeostatic remodeling are only partially understood. Two explanations, pertinent to the focus of this review, are low calcium and low vitamin D intakes. Both lead to elevated PTH secretion and, hence, to increased bone remodeling. Thus, it is logical and, in retrospect, predictable, that elevating calcium and vitamin D intakes should promptly decrease bony fragility. It is worth recalling that PTH secretion drops immediately when extra calcium and vitamin D are given, and bone resorption responds almost immediately as well.^[24] Thus, preexisting resorption cavities are filled in day by day, while new ones are being created at a reduced rate, leading to improved strength within days of starting remodeling-suppressive therapy.

But contemporary low intake of these 2 key nutrients can be only a part of the explanation for high remodeling. McKane and colleagues^[21] pushed total calcium intake in healthy postmenopausal women to 2400 mg/d, resulting in lowering the 24-hour average PTH concentration and the bone remodeling rate -- but only to premenopausal levels. However, if Parfitt is correct, this amount is still substantially higher than what is needed to maintain mechanical integrity of the skeleton.

Another possible explanation for excessive remodeling is the shift to a seed-based diet at the time of the agricultural revolution. Seed foods today account for about two thirds of the energy intake of the global population, while our hunter-gatherer ancestors typically got fewer than 5% of total calories from such sources. Seed foods are typically low in calcium and potassium and high in sulfur-containing amino acids; all 3 characteristics are known to increase PTH secretion. Abbott and colleagues,^[28] examining static remodeling indices in bones from pre- and postagricultural populations, found an approximate doubling of remodeling across the agricultural

revolution. In addition, the agricultural revolution, by producing surplus energy, permitted a human population explosion that forced migration to higher latitudes where vitamin D status became problematic.

Whether these factors, taken together, constitute a fully adequate explanation for the elevated remodeling of modern humans is uncertain. Nevertheless, the new appreciation of the importance of remodeling enhances the rationale for ensuring an adequate calcium intake.

The Gap Between Knowledge and Action

Despite the widespread acceptance of the importance of calcium by both the healthcare profession and the public, there is a large gap between that conviction and corresponding behaviors. The Surgeon General, in a report on bone health,^[9] specifically stated that "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 far below the amount recommended for optimal bone health." Later, the report adds "...the gap between what we know and its application in the community remains large and needs to be closed."

The size of the gap was demonstrated by Stafford and colleagues in a study of physician-patient office encounters.^[29] In 1994, just before the first US approval of a bisphosphonate for treatment of osteoporosis, 43% of physician-patient encounters for a diagnosis of osteoporosis included a recommendation for augmented calcium intake. Nine years later, the proportion had fallen by nearly half -- to only 23%.^[28]

Furthermore, recent household consumption data indicate that 40% of individuals taking a bisphosphonate consume no calcium supplements, and 33% take fewer than 1 tablet per day.^[30] Thus, by both measures, nearly three fourths of all individuals being treated for osteoporosis with an antiresorptive agent were not getting sufficient calcium. It is important to recall that all the efficacy trials for bisphosphonates used supplemental calcium, and the efficacy of those agents in the absence of adequate calcium intake is unknown.

Discordance Among Published Reports

Against this enhanced background of understanding of how calcium operates, it becomes relatively easy to discern reasons why different studies may seem to yield different and even conflicting results. But first, there are some basic inferential considerations that are generally applicable, and not peculiar to calcium or nutrition. To begin with, sample size is often misleading. The tendency is to be swayed more by a study of 10,000 individuals than by a study of 100. Yet, a finding in both of a *P* value of .001 means that both have exactly the same chance of being wrong. Moreover, the outcome of the smaller sample may actually be more interesting, because achieving

that level of significance in 100 persons requires a larger difference than in 10,000. Study size is important mainly for purposes of investigative power. Furthermore, large size, even when necessary, often means poor ability to manage the investigation (see "The Problem of Compliance").

Another consideration, also generally applicable, is the fact that study power is always limited and some trials are therefore bound to yield inconclusive results no matter how well designed and executed. A study power of 85%, which would be considered quite good in well-designed clinical trials, means that a real effect will be missed about one sixth of the time. Studies with negative findings, thus, disprove nothing. Such outcomes are to be expected, and the only way to draw a safe conclusion about the efficacy of an intervention is to evaluate the totality of the evidence.

There are also many structural reasons why a trial may truly fail. In the case of the recently published reports from trials that have reported no calcium effect, there are easily discernible causes for failure. Principal among them is the absence of a low calcium intake control group and failure to ensure adequate compliance with the supplement regimen. Both of these points will be further elaborated.

A Suitable Range of Intakes

A feature that distinguishes nutrients from pharmacologic agents is that nutrients often function in a threshold manner. In other words, the physiologic outcome associated with the nutrient improves as intake increases to some specific threshold value, above which further increases in intake produce no additional effect. A familiar example is the relationship between iron intake and circulating hemoglobin mass. If an individual with iron-deficiency anemia is given iron, hemoglobin rises. However, once blood hemoglobin reaches a value in the normal range, further increases in iron intake produce no further change in hemoglobin concentration.

Calcium functions in a similar manner. This phenomenon is depicted in Figure 3, which shows an idealized calcium threshold curve for normal adults.

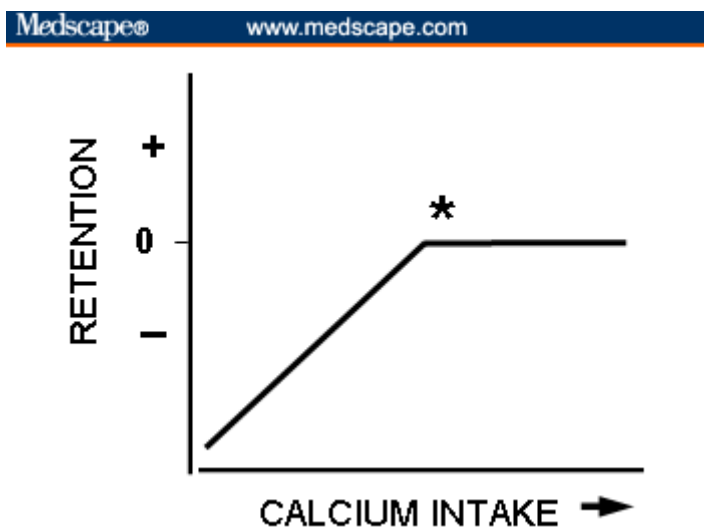


Figure 3. Calcium threshold curve for normal adults.

Retention curve for calcium expressed as a function of calcium intake in white adults. The threshold value, indicated by an asterisk, is the lowest intake that ensures that the skeleton will not be eroded to offset daily obligatory calcium losses. (Copyright Robert P. Heaney, 2006. Published with permission.)

At low intakes, calcium retention (equivalent to bone mass change) is negative; in other words, bone is being lost. However, at adequate intakes (to the right of the threshold point in Figure 3) calcium retention is zero and bone mass is maintained. However, no further retention occurs as more calcium is consumed -- one cannot store more calcium as bone than the skeleton requires for its current mechanical loading regimen, just as one cannot store extra iron as hemoglobin once erythropoietin secretion is minimized.

Figure 4 contrasts 2 scenarios of calcium intervention and shows why 1 of the contrast groups must always be substantially below the threshold if one wishes to determine whether there is a bony effect. This requirement would seem to go without saying, but it is often ignored. If the contrast groups in a controlled trial have calcium intakes that are both to the right of the inflection point of Figure 3 (or, equivalently, if the range of calcium intakes in an observational study is predominantly to the right of the threshold), then calcium intake would be predicted to show no association with the outcome chosen for study.

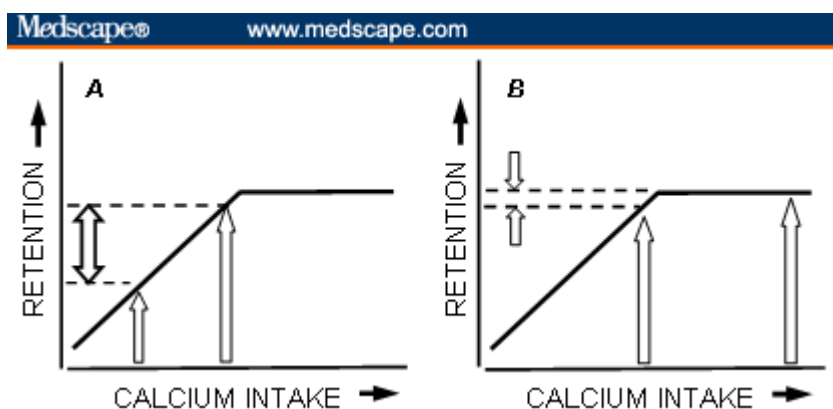


Figure 4. Calcium interventions.

A. Expected effect in a calcium intervention trial in which 1 of the contrast groups had calcium intake substantially below the threshold of Figure 1.

B. The corresponding depiction of a trial in which both contrast groups had intake near or above the effect threshold. (Copyright Robert P.

Heaney, 2006. Published with permission.)

This is at least a partial explanation why several randomized, controlled trials of bone effects of calcium have failed. One was a trial in men published several years ago.^[31] The group receiving the calcium achieved an average intake of over 2000 mg/d, while the control group had a calcium intake averaging 1159 mg/d. Despite the large difference in intake, 1159 mg was already above the recommended intake for the age

group. Thus, it was a virtual certainty that some, and perhaps most, of the individuals in the control group were already ingesting enough calcium to ensure the desired skeletal outcome. Hence, no apparent effect of additional calcium would be expected, which is precisely what the authors reported.

The same explanation applies to the recent publication of results from the calcium arm of the Women's Health Initiative,^[1] in which the placebo group had a mean calcium intake between 1100 and 1200 mg/d (ie, at or above the effect threshold). Although no significant difference in hip fracture rate by intention-to-treat was found, the authors did note that the observed fracture rate was only half what had been expected, consistent with expression of a calcium benefit in both groups. Moreover, per-protocol analysis showed a significant, 30% reduction in the number of fractures among adherent participants.

A very similar outcome was seen in another NIH-sponsored trial, Calcium in Preeclampsia Prevention (CPEP).^[32] Several randomized, controlled trials in developing countries had previously shown a striking reduction in preeclampsia incidence in women given calcium supplements during pregnancy.^[33,34] In these trials, the calcium intake of the control group was low. Because of the importance of preventing preeclampsia, a trial to confirm previous findings was subsequently conducted by the NIH. However, unlike in the prior trials, the calcium intake of the control group averaged 1135 mg/d, an intake actually above the current recommendation for pregnancy. When the results were analyzed, it was found that preeclampsia incidence was low in both groups and that there was no significant reduction in incidence in the calcium-supplemented arm of the study. One could have predicted that both groups would already have experienced the maximum benefit achievable from calcium, and that giving more calcium to one than to the other would have been without effect. Once again, this was exactly what was found.

This problem is not easy to solve. The seriousness of such disorders as preeclampsia and osteoporotic fracture are such that it would have been unethical to give a control group amounts less than those shown to prevent harm. In effect, adequately controlled, *confirmatory* trials cannot ethically be performed for most serious disease outcomes.

The Nutrient Being Evaluated Is Plausibly Limiting

Several factors affecting whether calcium intake may be limiting for a bony endpoint can be identified. These include exercise, hormonal status, general nutrition, race, and obesity.

In a meta-analysis of trials involving calcium and exercise, Specker and colleagues^[35] found that only individuals who actively exercised responded to calcium supplementation. It is also generally recognized that calcium supplements do not prevent disuse osteoporosis. Similarly, even large calcium supplements, although they may slow menopausal bone loss, do not prevent it or reduce the amount ultimately lost.^[36] All of these findings are due to the fact that prevailing calcium intake is not the limiting factor affecting bone mass; hence, altering it has little or no effect.

The same is true for general nutrition. Bone health is not a mono-nutrient issue. For example, nearly 50% of the volume of bone consists of protein, and bone remodeling requires a continuing supply of fresh dietary protein. Most, although not all, studies of nutrition and bone show a positive interaction of protein and calcium, and in 1 controlled trial of calcium and vitamin D supplementation, bone gain in response to the supplement was confined to individuals with higher protein intakes.^[37]

The same principles apply to vitamin D, long recognized as essential for calcium absorption. Although very high calcium intakes can overcome much of the absorptive block of vitamin D deficiency, the amounts needed are considerably in excess of calcium supplement doses used in most trials.^[38] Therefore, unrecognized vitamin D deficiency will also confound a trial of calcium. This is not merely a theoretical concern. Various population-based studies indicate that prevalence of inadequate vitamin D status is high,^[39] and in some groups nearly universal.^[40]

Racial groups have different calcium requirements for bone health, with blacks needing substantially less to build and maintain a healthy skeleton than whites.^[16] In reality, calcium intake in blacks, although lower than those of non-Hispanic whites, is nevertheless mainly to the right of their specific response thresholds (Figure 5). This phenomenon is independent of body mass index. In other words, inclusion of black participants in any study sample is likely to load both treatment and control groups with individuals who have already realized the full skeletal benefits of adequate calcium intake.

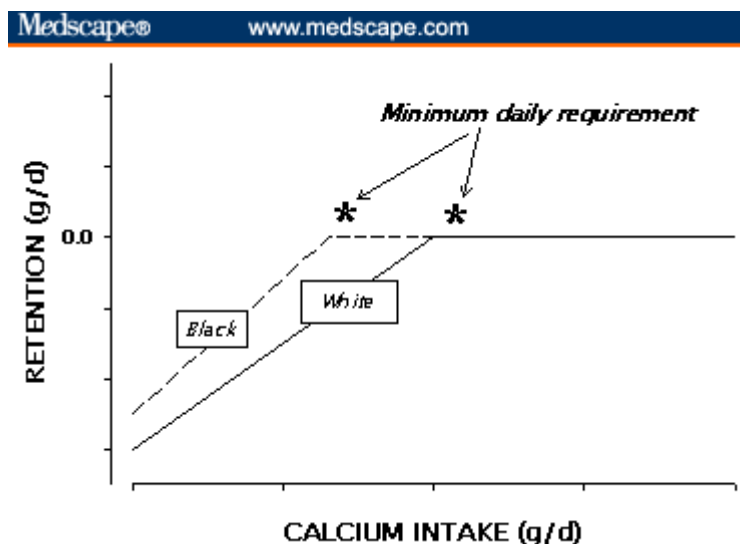


Figure 5. Response thresholds.

Intake and retention curve for calcium in blacks, superimposed on that for whites. The amount of the leftward shift is not known with certainty, but is probably on the order of 300-500 mg of calcium per day. (Copyright Robert P. Heaney, 2006. Published with permission.)

Obesity presents other interpretative challenges, particularly in light of the rising prevalence of this disorder and thus the likelihood that obese individuals will be included in many or most study samples. Obese women have larger, heavier

skeletons than do their normal-weight counterparts, and they lose less bone at menopause.^[41] The usual explanations (greater weight-bearing, peripheral synthesis of estrogen in fat cells) are not fully satisfying, as the greater bone density holds for both non-weight- and weight-bearing bones, and the effect seems to be independent of postmenopausal hormone replacement.^[42] In fact, the relationship between calcium intake and bone status in obesity is largely unknown and may confound studies of calcium nutrient effects. This relationship needs to be studied in its own right.

It could be argued that, generally, calcium nutrition is not a major problem for obese individuals or blacks. Although this may well be correct, at least for bone health, undoubtedly there will be those in both groups with intakes below their respective intake thresholds who could, therefore, benefit from increased intake. But the point here is that, if most such individuals have intakes above their thresholds, including them in study cohorts will load the cohorts with nonresponders and thus hinder finding a relationship that may be critically important for vulnerable population groups (eg, normal-weight, non-Hispanic whites).

The Problem of Compliance

Inadequate compliance with appropriate calcium supplementation regimens is a problem not only in clinical practice but in clinical trials as well and helps explain sometimes-discordant results. Studies that are so large as to preclude bonding between study participants and investigative staff are one cause of poor compliance. A good example is the RECORD trial,^[2] which was conducted by mail and required daily pill-taking for both calcium and vitamin D preparations. No fracture reduction was found, but the documented compliance rate was only about 40%, a figure supported by a rise in serum 25(OH) vitamin D that was only about half the expected amount for the vitamin D dose used.

Similarly, a second practice-based trial in the United Kingdom studying calcium and vitamin D reported no fracture reduction but had a compliance rate of only about 50%.^[3] Both studies concluded that calcium did not reduce fracture risk. Both, instead, should have concluded that the mode of augmenting calcium intake used by the study participants was ineffective.

Other Factors Important for Bone Health

In addition to calcium there are at least 3 other factors critical for bone health, particularly after mid-life: vitamin D, protein, and exercise.

Vitamin D. Although vitamin D status has been discussed as a potential confounder of results in calcium studies, the importance of vitamin D in its own right must also be emphasized. It has long been recognized that vitamin D is important for calcium absorption, and recent studies have demonstrated that absorption efficiency increases with improving vitamin D status up to serum 25(OH)D levels of about 80 nmol/L (32 ng/mL).^[43,44] Postmenopausal women, as reported in many studies, tend to have average serum 25(OH)D values ranging from 50 to 55 nmol/L (20 to 22 ng/mL)^[43,45] and are therefore absorbing the calcium they ingest with reduced efficiency.^[38,43]

In the sole fracture study that has evaluated this issue, raising serum 25(OH)D from the typical postmenopausal range up to 75 nmol/L resulted in a 33% reduction in all osteoporotic fractures combined.^[45] Among persons in this age range, vitamin D may be acting in several different ways in addition to promoting calcium absorption.^[46] Nevertheless, it is clear that inadequate vitamin D status reduces the benefit potentially achievable from an adequate calcium intake.

Protein. As with vitamin D, protein plays an important role in its own right. Although North Americans are considered to consume generous amounts of protein it is also true that many fragile elderly individuals have low protein intake. If these same individuals are our osteoporosis patients, then they will probably not respond well to pharmacotherapy until their nutritional status is repaired. If deficient in calcium, vitamin D, *and* protein, many will be unresponsive to monotherapy, whether nutritional or pharmacologic. This is seen most obviously in patients with hip fracture, whose outcomes have been shown to improve dramatically with protein supplementation.^[46]

Exercise. Bones are designed to bear loads and to resist mechanical forces. Maintenance of adequate bone mass requires continued mechanical loading. Nutrition alone may slow the progress of disuse bone loss, but it will not block its full, ultimate expression. Optimal exercise regimens are uncertain, but impact loading appears to be more osteotrophic than, for example, weight lifting or swimming. In general, patients with osteoporosis need to maintain as vigorous an exercise program as is compatible with their bone fragility status.

Dietary Calcium Sources

Calcium-rich foods include the dairy group (milk, hard cheese, yogurt, cottage cheese), broccoli, Chinese cabbage (bok choy), green leafy vegetables (kale, mustard, collards), sardines with bones (canned), dried fruit, nuts and seeds (figs, almonds, soy nuts), and pulses (peas, beans, and lentils). A number of calcium-fortified foods and drinks are also now available, including breakfast bars, cereals, breads, juices, and milk substitutes. An extensive list of the calcium content of foods is available online from the US Department of Agriculture.^[49]

Patients often erroneously believe that they are obtaining sufficient calcium through their diet. However, it is known that the median calcium intake in postmenopausal women in North America is substantially below existing recommendations.^[11] Because milk and milk products provide the majority of dietary calcium in the United States, if a person is lactose-intolerant, a vegan (consuming no animal products), or avoids dairy products for other reasons, it may be especially challenging to obtain adequate amounts of calcium solely through diet.^[50]

In addition to being aware of the amount of dietary calcium they are ingesting, it is important that patients understand that absorption from foods can be affected by a number of factors, many of which have already been well described. These include age, vitamin D, pregnancy, and plant substances in the diet.

Oxalates (found in chocolate and spinach) and phytate (found in whole grains) are among dietary substances that impair absorption. Therefore, 8 cups of spinach are

needed to obtain the same amount of calcium obtained from an 8-ounce serving of milk or 1 cup of yogurt, which contain calcium in an easily absorbable form.^[51]

Calcium from Supplements

For many patients, calcium supplements are the most appropriate choice to ensure adequate intake. A number of different calcium compounds are used in supplements; the 2 main forms are calcium carbonate and calcium citrate. Although absorption of calcium citrate is similar to calcium carbonate, a calcium carbonate supplement contains 40% calcium vs the 21% found in calcium citrate.^[52] Because formulations may contain different amounts of calcium, the number of tablets needed to obtain a recommended dose may vary. Figure 6 depicts the amount of calcium found in common compounds.

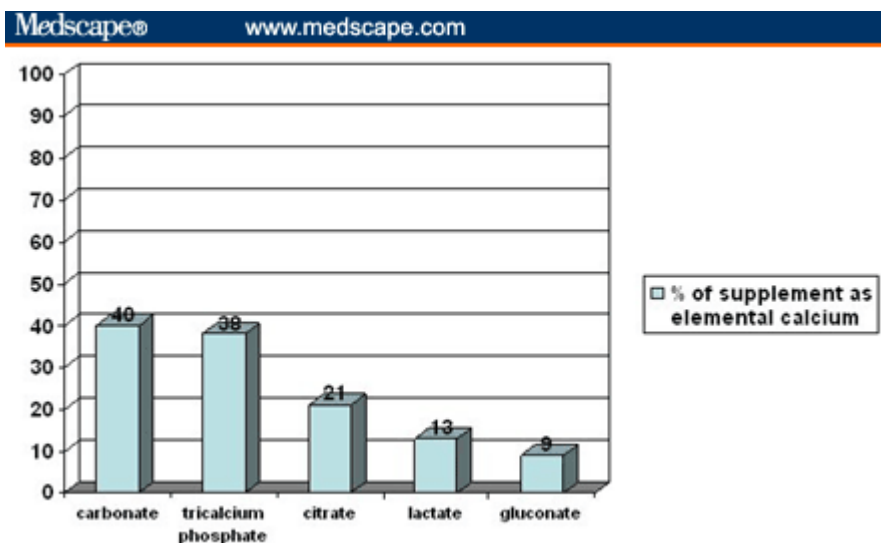


Figure 6. Percentage of calcium in supplement.
Source: Office of Dietary Supplements^[51]

When beginning supplementation, gradual intake is best -- taking less than 500 mg a day for a week -- followed by slowly adding calcium to achieve the recommended amount. Most supplements should be taken with food, as the slow gastric emptying following a meal optimizes calcium absorption. Although most brand-name calcium supplements are absorbed easily in the body, chewable and liquid calcium supplements dissolve most easily because they are broken down prior to entering the stomach.

Patients should also be told that calcium supplements can interact with prescription and over-the-counter medications. Medications that may interact with calcium include:^[51]

- digoxin;
- fluoroquinolones;
- levothyroxine;

- antibiotics in the tetracycline family;
- tiludronate disodium;
- anticonvulsants such as phenytoin;
- thiazide, type of diuretic;
- glucocorticoids;
- mineral oil or stimulant laxatives; and
- aluminum- or magnesium-containing antacids.

Ingesting too much calcium can cause hypercalcemia, kidney stones, milk-alkali syndrome, or interfere with absorption of other minerals (iron, zinc, magnesium, and phosphorus). Calcium citrate may be preferred as a calcium source if a patient is at high risk for stone formation.^[51] Although some believe that calcium supplementation causes constipation, the evidence base to support this is scant.

Choosing a Supplement

Patients frequently ask healthcare providers for a specific recommendation for which type of supplement to take. General considerations include purity and tolerance.^[53]

Purity. Supplements with familiar brand names are typically best. Labels on supplements should include the word "purified" or have the United States Pharmacopoeia (USP) symbol. Calcium from unrefined oyster shell, bone meal, or dolomite without the USP symbol should be avoided, because high levels of lead or other toxic metals may be present.

Tolerance. A calcium supplement may be associated with side effects such as constipation. If simple measures (such as increasing intake of fluids and fiber) do not resolve the problem, another calcium supplement should be tried.

Specific questions to be considered by patients in choice of a supplement include:^[53]

- Is it convenient -- can they remember to take it as frequently as recommended?
- Is the cost of the supplement within budget?
- Is it widely available?

Good online sources of information for patients about calcium and or bone health include the National Institutes of Health, Office of Dietary Supplements;^[51] American Osteoporosis Foundation,^[54] and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.^[53]

Conclusion

The totality of the evidence indicates that high calcium intake is important both for prevention and management of osteoporosis, and recent negative trials do not refute the much larger body of positive studies. The challenge is not to haggle over exactly

how much is enough but, as the Surgeon General's report on osteoporosis put it, to recognize that current intake is far below optimal values. It is imperative to take action to augment calcium intake, both in the general population and particularly in persons being treated for osteoporosis.

Supported by an independent educational grant from Sanofi-Aventis.

References

1. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med*. 2006;354:669-683. [Abstract](#)
2. Grant AM. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomized placebo-controlled trial. *Lancet*. 2005;365:1621-1628. [Abstract](#)
3. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of supplementation with calcium and cholecalciferol (vitamin D3) for prevention of fractures in primary care. *BMJ*. 2005;330:1003-1006. [Abstract](#)
4. Consensus Conference on Osteoporosis. *JAMA*. 1994;252:799-802.
5. Consensus Conference on Optimal Calcium Intake. *JAMA*. 1994;272:1942-1948. [Abstract](#)
6. NIH Consensus Statement on Osteoporosis Prevention, Diagnosis and Therapy. Vol. 17, Number 1, March 2000. Available at: <http://www.consensus.nih.gov/2000/2000Osteoporosis111html.htm> Accessed March 23, 2006.
7. Dietary Reference Intakes for Calcium, Magnesium, Phosphorus, Vitamin D, and Fluoride. Food and Nutrition Board, Institute of Medicine. National Academy Press, Washington, DC, 1997.
8. US Department of Agriculture. Dietary guidelines for Americans. Available at: www.health.gov/dietaryguidelines Accessed March 23, 2006.
9. DHHS. Bone health and osteoporosis: a report of the Surgeon General. PHS; 2004.
10. NIH News. Calcium and Vitamin D supplements offer modest bone improvements, no benefits for colorectal cancer. Press release February 15, 2006. Available at: <http://www.nhlbi.nih.gov> Accessed March 10, 2006.
11. Alaimo K, McDowell MA, Briefel RR, et al. Dietary intake of vitamins, minerals, and fiber of persons 2 months and over in the United States: Third National Health and Nutrition Examination Survey, Phase 1, 1988-91. Advance data from vital and health statistics; no. 258. Hyattsville, Maryland: National Center for Health Statistics, 1994.
12. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. *N Engl J Med*. 1992;327:1637-1642. [Abstract](#)

13. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med.* 1997;337:670-676. [Abstract](#)
14. Chevalley T, Rizzoli R, Nydegger V, et al. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. *Osteoporos Int.* 1994;4:245-252. [Abstract](#)
15. Recker RR, Hinders S, Davies KM, et al. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *J Bone Miner Res.* 1996;11:1961-1966. [Abstract](#)
16. Nordin BEC, Polley KJ, Need AG, Morris HA, Marshall D. The problem of calcium requirement. *Am J Clin Nutr.* 1987;45:1295-1304. [Abstract](#)
17. Klesges RC, Ward KD, Shelton ML, et al. Changes in bone mineral content in male athletes. *JAMA.* 1996;276:226-230. [Abstract](#)
18. Eaton B, Nelson DA. Calcium in evolutionary perspective. *Am J Clin Nutr.* 1991;54:281S-287S. [Abstract](#)
19. Cummings SR, Karpf DB, Harris F, et al. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. *Am J Med.* 2002;112:281-289. [Abstract](#)
20. Chapurlat RD, Palermo L, Ramsay P, Cummings SR. Risk of fracture among women who lose bone density during treatment with alendronate. The Fracture Intervention Trial. *Osteoporosis Int.* 2005;16:842-848. [Abstract](#)
21. McKane WR, Khosla S, Egan KS, Robins SP, Burritt MF, Riggs BL. Role of calcium intake in modulating age-related increases in parathyroid function and bone resorption. *J Clin Endocrinol Metab.* 1996;81:1699-1703. [Abstract](#)
22. Wastney ME, Martin BR, Peacock M, et al. Changes in calcium kinetics in adolescent girls induced by high calcium intake. *J Clin Endocrinol Metab.* 2000;85:4470-4475. [Abstract](#)
23. Maricic M, Adachi JD, Sarkar S, Wu W, Wong M, Harper KD. Early effects of raloxifene on clinical vertebral fractures at 12 months in postmenopausal women with osteoporosis. *Arch Intern Med.* 2002;162:1140-1143. [Abstract](#)
24. Roux C, Seeman E, Eastell R, et al. Efficacy of risedronate on clinical vertebral fractures within six months. *Curr Med Res Opin.* 2004;20:433-439. [Abstract](#)
25. Heaney RP: Is the paradigm shifting? *Bone.* 2003;33:457-465.
26. Recker RR, Lappe JM, Davies KM, Heaney RP. Bone remodeling increases substantially in the years after menopause and remains increased in older osteoporosis patients. *J Bone Miner Res.* 2004;19:1628-1633. [Abstract](#)
27. Parfitt AM. What is the normal rate of bone remodeling? *Bone.* 2004;35:1-3
28. Abbott S, Trinkaus E, Burr DB. Dynamic bone remodeling in later Pleistocene fossil hominids. *Am J Phys Anthropol.* 1996;99:585-601. [Abstract](#)
29. Stafford RS, Drieling RL, Hersh AL. National trends in osteoporosis visits and osteoporosis treatment, 1988-2003. *Arch Intern Med.* 2004;164:1525-1530. [Abstract](#)

30. Heaney RP. Proctor and Gamble Pharmaceuticals. Unpublished data.
31. Orwoll ES, Oviatt SK, McClung MR, Deftos LJ, Sexton G. The rate of bone mineral loss in normal men and the effects of calcium and cholecalciferol supplementation. *Ann Intern Med.* 1996;124:187-196. [Abstract](#)
32. Levine RJ, Hauth JC, Curet LB, et al. Trial of calcium to prevent preeclampsia. *N Engl J Med.* 1997;337:69-76. [Abstract](#)
33. Belizan JM, Villar J, Gonzalez L, Bergel L. Calcium supplementation to prevent hypertensive disorders of pregnancy. *N Engl J Med.* 1991;325:1399-1405. [Abstract](#)
34. Bucher HC, Guyatt GH, Cook RJ, et al. Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia. A meta-analysis of randomized controlled trials. *JAMA.* 1996;275:1113-1117. [Abstract](#)
35. Specker BL. Evidence for an interaction between calcium intake and physical activity on changes in bone mineral density. *J Bone Miner Res.* 1996;11:1539-1544. [Abstract](#)
36. Elders PJM, Netelenbos JC, Lips P, et al. Calcium supplementation reduces vertebral bone loss in perimenopausal women: a controlled trial in 248 women between 46 and 55 years of age. *J Clin Endocrinol Metab.* 1991;73:533-540. [Abstract](#)
37. Dawson-Hughes B, Harris SS. Calcium intake influences the association of protein intake with rates of bone loss in elderly men and women. *Am J Clin Nutr.* 2002;75:773-779. [Abstract](#)
38. Heaney RP. Vitamin D: Role in the calcium economy. In: Feldman D, Glorieux FH, Pike JW, eds. *Vitamin D.* 2nd ed. San Diego: Academic Press; 2005:773-787.
39. Holick MF, Siris ES, Binkley N, et al. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab* (Epub ahead of print, March 29, 2005).
40. Passeri G, Pini G, Troiano L, et al. Low vitamin D status, high bone turnover, and bone fractures in centenarians. *J Clin Endocrinol Metab.* 2003;88:5109-5115. [Abstract](#)
41. Ribot C, Tremollieres F, Pouilles JM, Bonneu M, Germain F, Louvet JP. Obesity and postmenopausal bone loss: the influence of obesity on vertebral density and bone turnover in postmenopausal women. *Bone.* 1998;8:327-331.
42. Heaney RP, Barger-Lux MJ, Davies KM, Ryan RA, Johnson ML, Gong G. Bone dimensional change with age: interactions of genetic, hormonal, and body size variables. *Osteoporos Int.* 1997;7:426-431. [Abstract](#)
43. Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. *J Am Coll Nutr.* 2003;22:142-146. [Abstract](#)
44. Heaney RP. The vitamin D requirement in health and disease. *J Steroid Biochem Mol Biol.* 2005;97:13-19. [Abstract](#)
45. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women

- living in the community: randomized double blind controlled trial. *BMJ*. 2003;326:469-474. [Abstract](#)
46. Bischoff HA, Dawson-Hughes B, Willett WC, et al. Effect of vitamin D on falls. *JAMA*. 2004;291:1999-2006. [Abstract](#)
 47. Heaney RP, Bachmann GA. Interpreting studies of nutritional prevention. A perspective using calcium as a model. *J Women' Health*. 2005;14:990-997.
 48. Delmi M, Rapin CH, Bengoa JM, Delmas PD, Vasey H, Bonjour JP. Dietary supplementation in elderly patients with fractured neck of the femur. *Lancet*. 1990;335:1013-1016. [Abstract](#)
 49. United States Department of Agriculture. USDA national nutrient database. Available at:
<http://www.nal.usda.gov/fnic/foodcomp/Data/SR17/wtrank/sr17w301.pdf>
Accessed March 20, 2006.
 50. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, vitamin D and fluoride. Washington DC: The National Academies Press, 1997.
 51. Office of Dietary Supplements. Dietary supplement fact Sheet: calcium. Available at: <http://dietary-supplements.info.nih.gov/factsheets/calcium.asp>
Accessed March 20, 2006.
 52. Levenson D, Bockman R. A review of calcium preparations. *Nutr Rev*. 1994;52:221-232. [Abstract](#)
 53. National Institute of Arthritis and Musculoskeletal and Skin Diseases. Calcium supplements: What to look for. Available at:
http://www.niams.nih.gov/bone/hi/calcium_supp.htm Accessed March 20, 2006.
 54. National Osteoporosis Foundation. How can I prevent osteoporosis? Available at: <http://www.nof.org/prevention/index.htm> Accessed March 20, 2006.