Calcium and Vitamin D in the Prevention and Treatment of Osteoporosis: Shedding Light on New Developments

Ian B. Hollis, PharmD, BCPS, and Randolph E. Regal, BS, PharmD

Educational Objectives

After reviewing this article, readers should be able to:

- Review the physiological role of calcium and vitamin D.
- Explain the importance of and the differences in calcium and vitamin D oral supplement formulations.
- Describe the effect of calcium and vitamin D on bone mineral density and fracture risk.

Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength, which ultimately predisposes individuals to an increased risk of fracture. The disorder results from a disturbance in the bone-remodeling cycle, whereby bone resorption exceeds bone formation. This bone loss and skeletal fragility then predispose individuals to the increased risk of fractures, most commonly involving the hip, wrist, and vertebrae.1-3

Fractures are accompanied by considerable morbidity and mortality and are a source of substantial health care expenditures. Estimated direct costs associated with fractures resulting from osteoporosis are as high as $10 billion to $15 billion per year in the U.S. when indirect costs are included, values in a single year have been as high as $94 billion.4,5 In 1990, 1.3 million to 1.7 million hip fractures occurred worldwide. By the middle of the 21st century, this number is expected to increase steadily to six million per year.5,6

Common risk factors for osteoporosis and subsequent fracture include Caucasian or Asian descent, early menopause, physical inactivity, cigarette smoking, excessive alcohol consumption, low body mass index (BMI), chronic steroid therapy, and hypogonadism. Another significant risk factor is an individual's nutritional status, especially with respect to vitamin D and calcium intake and utilization.7,8

In this article, we discuss the newest concepts in the literature as they relate to the pharmacology, clinical efficacy, and toxicity of calcium and vitamin D in preventing and treating osteoporosis. Today, optimal medical management of this disease includes the additional use of antiresorptive agents such as bisphosphonates, selective estrogen receptor modulators (SERMs), calcitonin, and osteoblast-stimulating agents such as teriparatide (Forteo, Lilly).3,9 However, these topics are addressed in other texts and reviews and are not discussed within the context of this article.

Calcium Homeostasis

Calcium is an integral component of bone structure and strength. Approximately 99% of the body's calcium stores are found in bone; the remaining 1% circulates in the blood, where it is bound either to plasma proteins or occurs in its freely ionized form.10 Skeletal bone serves as a reservoir for calcium when it is needed for other bodily functions such as muscle contraction and nerve transmission.

When the circulating concentration of calcium falls below the normal reference range of 8.5 to 10.5 mg/dL, parathyroid hormone (PTH) is released from parathyroid glands to correct this fluctuation.11 PTH acts via several mechanisms:

- increased reabsorption of calcium in the kidney tubules
- increased renal production of the active form of vitamin D: 1,25(OH)₂D (calcitriol)
- stimulation of osteoclasts

Osteoclasts are large, macrophagic cells responsible for bone resorption.9 These cells bind to bone, releasing hydrogen ions and proteolytic enzymes that dissolve its organic components, thereby liberating calcium for use in body processes while also decreasing bone mineral density (BMD). The effects of vitamin D on calcium homeostasis are discussed later. Figure 1 illustrates this homeostatic system.
Because of this “saturation phenomenon,” in terms of how much calcium can be absorbed by the intestine at one time, it has generally been recommended that no single calcium dose should exceed 500 to 600 mg of elemental calcium (e.g., the amount of calcium in a supplement that is available for the body to absorb). Until recently, this idea was thought to apply to every form of calcium. However, more recent evidence shows that unlike calcium carbonate, calcium citrate forms a soluble complex that can be passively absorbed and can thus circumvent this saturable transcellular active transport process. Consequently, the absorption of calcium carbonate is more likely than the citrate salt to be affected by vitamin D stores, and it is more likely to display dose-dependent absorption.

In clinical terms, the absorption characteristics of calcium citrate make it a more likely candidate for dose-consolidation regimens in which only one or two doses need to be given in order to meet the usual goal of 1,000 to 1,500 mg of elemental calcium per day, the recommended intake established by the National Academy of Sciences and the National Institutes of Health (NIH). Under this guideline, it seems appropriate that one could consolidate calcium citrate products that contain 315 mg of elemental calcium (e.g., calcium citrate with vitamin D) by giving two tablets at a time; however, more data are needed to determine whether single doses of calcium carbonate beyond this level can be given without significantly compromising bioavailability.

Oral Calcium Preparations and Their Bioavailability: Passing the Acid Test?

Numerous oral calcium formulations are on the market (Table 1). These formulations differ primarily in their companion anion, which consequently imparts their physiochemical properties. These preparations vary in their fractional content of calcium by weight (elemental calcium), ranging from calcium carbonate at 40% to calcium gluconate at only 9.3%. However, neither this factor nor the solubility of these varying salt forms is the sole determinant of bioavailability.

Heaney et al. showed that the degree of dietary calcium absorption was largely independent of the solubility of the salt form and concluded that two of the most commonly used oral supplemental calcium salt forms (citrate and carbonate) were bioequivalent. This assertion, however, correlates poorly with the evidence presented in this article. It is important to consider the specific mechanisms of calcium absorption and the effects of different calcium forms in order to optimize calcium supplementation.

**Calcium Absorption**

Calcium enters the body by crossing the epithelial surface of the gastrointestinal (GI) tract in a combination of passive and active processes. Calcium traverses the tight junctions between enterocytes and passively diffuses down its electrical and concentration gradient in paracellular transport, a process that occurs throughout the length of the intestinal tract. The complementary active calcium absorption mechanism is transcellular transport, which takes place predominantly in the duodenum and upper jejunum. Transcellular transport is a protein-mediated process that is driven by vitamin D and assumes a larger role in calcium absorption when dietary calcium intake is low.

Thus, the absorption of calcium is predominantly via an active transport mechanism in the GI tract. It has always been assumed that only the free calcium ion was absorbed via this process. The amount of calcium absorbed by the body depends on factors such as ethnicity, sex, age, vitamin D stores, and the amount of calcium ingested. As the calcium load increases and vitamin D stores decrease, less ionic calcium is able to be absorbed by the active transport process.

**Table 1 Oral Calcium Supplements**

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Salt Form</th>
<th>Calcium Content (by Weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkalak, Alka-Mints, Amitone, Calcarb, Calci-Chew, Cal-Mint, Calci-Mix, Calgest, Caltrate, Chooz, Florical, OsCal, Oysco, Titralac, Tums</td>
<td>Calcium carbonate</td>
<td>40%</td>
</tr>
<tr>
<td>Cal-Citrate, Citracal</td>
<td>Calcium citrate</td>
<td>24.1%</td>
</tr>
<tr>
<td>N/A</td>
<td>Calcium formate</td>
<td>30.8%</td>
</tr>
<tr>
<td>Cagluc</td>
<td>Calcium gluconate</td>
<td>9.3%</td>
</tr>
<tr>
<td>Phos-Lo</td>
<td>Calcium acetate</td>
<td>25%</td>
</tr>
</tbody>
</table>
with other controlled trials of the relative bioavailability of these two salts. Harvey et al. gave radiolabeled calcium supplements of both salt forms to a small group of healthy women. The researchers observed that citrate was better absorbed than carbonate (39.2 ± 8.6% vs. 31.2 ± 9.4%; P < 0.001). Hansen et al. showed a significantly greater absorption of citrate solution than carbonate solution in middle-aged men but found no difference in absorption between citrate suspension and carbonate solution.

When Heller et al. gave citrate and carbonate supplements with breakfast to 18 healthy patients, the increase in both the serum calcium concentration and the calcium area-under-the-curve (AUC) concentration (measured up to six hours after the dose) observed in the citrate group was significantly greater than in the carbonate group.

Hanzlik and Harvey and their colleagues also found a more pronounced increase in serum calcium levels and a greater urinary calcium excretion, respectively, in patients receiving citrate. In the latter of these two studies, a subgroup of patients was analyzed specifically for the relative bioavailability of the two agents. The citrate form was absorbed at a rate of 40.2 ± 6.7%, compared with 31.4 ± 1% for carbonate. Thus, more studies suggest a somewhat greater bioavailability of calcium citrate than calcium carbonate in a variety of patient populations.

With many patients now taking potent acid-lowering agents such as proton pump inhibitors (PPIs), more attention is being paid to the relative bioavailability of calcium salts in low-acid environments. In one case–control study, the use of PPIs for hip fractures, and the relationship was related to the dose of the PPI. In the authors’ discussion, they cited calcium malabsorption as the most likely culprit for this adverse outcome.

Calcium carbonate is relatively insoluble at neutral pH and therefore needs to be in an acidic environment to ensure optimal absorption. Conversely, as confirmed in one study comparing the bioavailability of citrate and carbonate in achlorhydric patients, the absorption of the citrate salt does not appear to be reduced in this setting.

One prospective randomized, placebo-controlled, crossover, double-blind study directly addressed calcium absorption and PPIs in community-dwelling elderly women over 65 years of age. After seven days of taking omeprazole (Prilosec, AstraZeneca) 20 mg once daily, calcium carbonate absorption was reduced by 41% (95% confidence interval [CI], −86% to 3%), compared with placebo. In the study, patients took their calcium supplement on an empty stomach after an overnight fast. Although the findings were not conclusive, some experts believe that taking calcium with food (thus increasing stomach acid secretion) may improve absorption in these relatively achlorhydric environments. More data are needed on comparative studies between the two salts in the milieu of PPI use, but the current evidence points toward a preference to use the citrate salt in patients who need to be maintained on long-term PPI regimens. This would be especially true for patients who do not ingest full or regular meals when they take calcium supplements.

One exception to the “if on a PPI, use calcium citrate” adage might pertain to patients on hemodialysis or other patients with severe renal impairment. The citrate salt enhances aluminum absorption, thereby potentiating the aluminum-related neurotoxicity and osteoporosis sometimes seen in this patient population. Calcium acetate, which is more water-soluble and already marketed as a phosphate binder for end-stage renal disease (ESRD), is also thought to be well absorbed in low-acid environments, especially when it is taken with meals. Therefore, calcium acetate should be the calcium supplement of choice for patients with ESRD who are taking PPIs. The usual dose of six calcium acetate tablets daily yields almost 1 g of elemental calcium.

### Optimal Daily Calcium Dosage and Timing

The elevation of parathyroid hormone (PTH) levels in response to below normal serum calcium levels has a deleterious effect on bone mineral density (BMD). In this situation, calcium is leached from bone to supplement the hypocalcemic condition. Oral calcium can suppress this elevation, but establishing an optimal calcium dose for this purpose is still challenging.

Although the data indicate some degree of variability in potency, substantial suppression of PTH secretion with oral calcium supplementation has been achieved with single doses as low as 250 mg. (We are expressing all doses of calcium products as elemental calcium.) Greater suppression of PTH secretion occurs with higher singular calcium doses, but the ability of the GI tract to tolerate single doses as high as 1,000 to 2,000 mg might be a concern.

Another consideration with oral calcium supplementation is the timing of doses. PTH secretion and other biochemical markers of bone resorption such as collagen breakdown products have a circadian rhythm that peaks at night. Blumsohn et al. found that 1,000 mg of calcium administered at 2300 hours (11 p.m.) was superior at blunting the typical nighttime increase in PTH compared with the same dose given at 0800 hours (8 a.m.). However, the accompanying decrease in the 24-hour urinary recovery of bone breakdown products in the group taking calcium at 11 p.m. did not achieve statistical significance.

Karkkainen et al. did not find a significant 24-hour difference in suppression of PTH secretion between groups receiving equal amounts of calcium at 9 a.m., compared with 9 p.m., although both calcium groups were superior to placebo. This study failed to show a difference in bone resorption markers in either group compared with placebo.

In a study by Scopacasa et al., calcium carbonate 500 mg twice daily and 1,000 mg once daily, when given to early postmenopausal women, reduced 24-hour markers of bone resorption by approximately 6% to 10% over placebo. This reduction was similar between treatment groups. No PTH values were measured as part of this study.

These results loosely correlated with the work of Ginty et al. In the Ginty study, a 14% to 16% reduction in bone resorption markers over placebo was observed in women receiving 400 mg of calcium (as lactate gluconate and carbonate) twice daily in addition to diet containing 800 mg of calcium. This study also lacked data on PTH.

In a study by Fardellone et al., calcium carbonate 600 mg...
twice daily produced decreases in markers of bone resorption by 16% to 18%.40

On the basis of these studies and in conjunction with current National Academy of Sciences and NIH recommendations for calcium intake for men and women,3 although it may depend on the calcium salt, a daily regimen of 1,000 to 1,500 mg of elemental calcium, divided twice daily, seems to optimize the efficiency of calcium absorption and may provide a significant suppression of PTH and markers of bone resorption during most of the day. Daily doses that exceed these current standards probably provide marginal incremental reductions in markers for PTH and may bring with them problems of increased cost, decreased tolerance, and reduced compliance. As we discuss later, far greater advantages may be gained by optimizing concomitant vitamin D than by pushing the calcium dose to higher levels.

Table 2  Effect of Isolated Calcium Supplementation on Bone Mineral Density (BMD): Summary of Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Post-menopausal Age (Cohort Span)</th>
<th>Elemental Calcium Supplement Dose (Daily)</th>
<th>Total Oral Calcium Intake (Daily)</th>
<th>Study Duration</th>
<th>Site of BMD Measurement</th>
<th>Site of Significant Benefit on BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recker et al.49</td>
<td>1977</td>
<td>7.7–10.2 years</td>
<td>1,040 mg</td>
<td>1,543 mg</td>
<td>2 years</td>
<td>Distal radius, metacarpals</td>
<td>Metacarpals</td>
</tr>
<tr>
<td>Riis et al.50</td>
<td>1987</td>
<td>15.8–19.9 months</td>
<td>2,000 mg</td>
<td>NA</td>
<td>2 years</td>
<td>Proximal forearm, distal forearm, lumbar spine, entire skeleton,</td>
<td>Proximal forearm</td>
</tr>
<tr>
<td>Polley et al.51</td>
<td>1987</td>
<td>7.7–9.0 years</td>
<td>1,000 mg</td>
<td>1,658 mg</td>
<td>9 months</td>
<td>Forearm</td>
<td>Forearm</td>
</tr>
<tr>
<td>Dawson-Hughes et al. 41</td>
<td>1990</td>
<td>3.2–13.0 years</td>
<td>500 mg</td>
<td>≥900 – ≥1,350 mg‡</td>
<td>2 years</td>
<td>Lumbar spine, femoral neck, distal radius</td>
<td>Femoral neck, distal radius⁵</td>
</tr>
<tr>
<td>Elders et al. 52</td>
<td>1991</td>
<td>1–1.4 years</td>
<td>1,000 mg or 2,000 mg</td>
<td>2,150 mg or 3,150 mg</td>
<td>2 years</td>
<td>Lumbar spine, metacarpals</td>
<td>Lumbar spine†</td>
</tr>
<tr>
<td>Reid et al.44</td>
<td>1993</td>
<td>9–10 years</td>
<td>1,000 mg</td>
<td>1,740 mg</td>
<td>2 years</td>
<td>Total body, lumbar spine, femoral neck, Ward’s triangle, trochanter</td>
<td>Total body, lumbar spine, Ward’s triangle</td>
</tr>
<tr>
<td>Aloia et al. 53</td>
<td>1994</td>
<td>1.6–2.0 years</td>
<td>1,700 mg</td>
<td>2,192 mg</td>
<td>2.9 years</td>
<td>Spine, femoral neck, radius,</td>
<td>Femoral neck</td>
</tr>
<tr>
<td>Recker et al. 42</td>
<td>1996</td>
<td>NA</td>
<td>1,200 mg</td>
<td>1,618 mg</td>
<td>4.3 ± 1.1 years</td>
<td>Distal radius</td>
<td>Distal radius‡</td>
</tr>
<tr>
<td>Chevalley et al. 46</td>
<td>1994</td>
<td>NA</td>
<td>800 mg</td>
<td>1,409 mg</td>
<td>1.5 years</td>
<td>Femoral shaft, femoral neck, lumbar spine</td>
<td>Femoral shaft, lumbar spine‡</td>
</tr>
<tr>
<td>Storm et al. 43</td>
<td>1998</td>
<td>NA</td>
<td>1,000 mg</td>
<td>1,633 mg</td>
<td>2 years</td>
<td>Greater trochanter, lumbar spine, femoral neck</td>
<td>Greater trochanter, lumbar spine, femoral neck</td>
</tr>
</tbody>
</table>

* In addition, the spine in women with low baseline calcium intake who received calcium citrate.
† During the first year of treatment.
‡ In patients with prevalent fracture.
NA = not available.

Effect of Isolated Calcium Supplementation on Bone Mineral Density and Fracture Reduction

As mentioned previously, the present-day prevention and treatment of osteoporosis involves combination therapy with calcium, vitamin D, and antiresorptive or osteoblast-stimulating agents. But what of patients who cannot afford or tolerate these newer therapies? Indeed, several studies have explored the ability of oral calcium supplementation alone to suppress or even to reverse BMD loss. These studies were conducted predominantly in postmenopausal women,41–44,46,48–53 the patient group of primary interest, and are worthy of scrutiny. Most of the literature suggests that some degree of BMD preservation seems to be attained with oral calcium supplementation. However, a closer look at the methods and results of the individual studies, summarized in Table 2, yields some conflicting results in relation to this generalization.

One major source of the difference in responses to calcium among various groups of women may be baseline calcium
intake. Among a “late-menopause” subgroup explored by Dawson-Hughes et al., nearly every group studied showed slower BMD loss when the baseline calcium consumption was 400 mg/day or less. The women consuming from 400 to 650 mg/day, when given calcium supplements, showed no BMD improvement at any site when compared with placebo, a compelling finding.

In a 1996 study by Recker et al., increases in forearm BMD were significant with 1,200 mg of calcium per day in the “previous fracture” cohort but not in the cohort without prior fractures. Despite a baseline calcium intake that appeared to be uniformly poor (approximately 420 mg/day), the authors attributed this effect to a lesser baseline BMD attributable to “nutritional calcium deficiency” in the former group, compared with the latter.

In a study by Storm, a calcium intake of less than 800 mg was a criterion for inclusion; as noted previously, the effects of oral calcium supplementation on BMD were robust. This left Reid and colleagues as the only investigators who observed no difference in results among women when they were classified according to their baseline calcium intakes. Thus, even though the findings are inconclusive, it appears that the women with the poorest diet in terms of daily calcium intake stand to benefit the most from calcium supplementation.

In contrast to studies that evaluated calcium benefits in terms of BMD, few trials have explored the rate of incident fractures. The NHANES I Epidemiologic Follow-up Study observed both men and women for a mean of 14.6 years and assessed the rate of incident fractures on the basis of quartiles (0%–25%, 26%–50%, 51%–75%, and 76%–100%) of dietary calcium intake. The relative risk of hip fracture was lower in the subjects consuming the higher three quartiles of calcium, but the findings were not statistically significant and did not result in a linear trend.

In Recker’s randomized, controlled trial of patients with poor calcium intake at baseline, a statistically significant decrease in repeated vertebral fractures was noted with 1,200 mg of oral calcium supplementation daily for 4.3 years. Chevalley et al. showed a significant decrease in the rate of vertebral fractures in patients who had been randomly assigned to receive 800 mg of oral calcium daily.

In a randomized study of patients receiving 1,200 mg of calcium carbonate daily or placebo, Prince et al. noted that the risk of fractures at all sites decreased by an impressive rate of 34% in patients taking at least 80% of their doses. This effect was even more impressive, considering their baseline calcium intake of about 900 mg daily.

The only trial to deviate from this trend, by Peacock et al., found that 750 mg of elemental calcium daily had no statistically significant effect, when compared with placebo, on the rate of all fractures.

Although the data on fracture prevention seem to favor the benefit of calcium supplementation, the data on BMD are equivocal. Unfortunately, the lack of consistent effect in these studies may be a result of factors beyond simple calcium availability, such as the presence of calcium-regulating hormones. A venture into the data concerning vitamin D supplementation may yield some clarity on this issue.

### Calcium Regulation by Vitamin D

One of the primary controls of calcium homeostasis is calcitriol, the physiologically active form of vitamin D. Humans obtain vitamin D either from subcutaneous photoconversion of 7-dehydrocholesterol in response to sunlight exposure or from dietary sources such as fortified milk, fatty fish, sardines, or eggs. However, 7-dehydrocholesterol (provitamin D₃) is an inactive compound that requires two sequential enzymatic hydroxylations to be converted to calcitriol.

The first conversion is accomplished by the liver to 25-hydroxyvitamin D (25-OH-D [calcidiol]) and then by the kidney to 1,25-dihydroxyvitamin D, or 1,25(OH)₂D (calcitriol) (Figure 2). The extent of kidney hydroxylation is modulated by PTH, which is affected by the body’s calcium stores. Enzymatic activity is low during periods of calcium repletion; it is increased when enhanced calcium absorption is required.

After calcitriol is formed, it helps reverse low serum calcium levels by binding to the vitamin D receptor (VDR) in its effector cells. This receptor binding induces gene expression,
which increases the synthesis of calcium transport proteins. Consequently, calcitriol activity increases the efficiency of calcium absorption at each major step in the transcellular intestinal absorption process.12

**Prevalence of Vitamin D Deficiency**

In light of the high incidence of osteoporosis today and the prominent regulatory role of vitamin D in the absorption of calcium, it should come as no surprise that the prevalence of vitamin D deficiency is substantial. Nutritional vitamin D status is determined by circulating blood levels of 25-OH-D.54 Although the precise definition of vitamin D “adequacy” or “deficiency” may vary according to the currently accepted sources, the prevalence of this malady appears profound.

After assessing the vitamin D status of 212 patients at a South Florida outpatient clinic, Levis et al.55 found that winter-time 25-OH-D levels averaged 24.9 ± 8.7 ng/mL in men and 22.4 ± 8.2 ng/mL in women. Using levels of 20 ng/mL or less as indicative of vitamin D deficiency, these investigators found a prevalence of 38% in men and 40% in women.

In a study of more than 1,500 women across the U.S. and Canada by Holick et al.,56 the rate of 25-OH-D levels at 20 ng/mL or below was 18%.

Vieth et al.57 assessed the seasonal variation in 25-OH-D status of Canadian women. Of all women included in the study, 20% to 30% had levels of 16 ng/mL or less during the winter months. This rate improved substantially, although not completely, in summer months.

The problem of vitamin D deficiency is not confined to North America. In fact, most of the literature characterizing this problem has been published outside the U.S.

Hill et al.58 characterized the late winter prevalence of 25-OH-D levels at 20 ng/mL or less in postmenopausal Irish women to be 46%, a figure that remained worrisome at 17% in late summer. Chapuy et al.59 determined the prevalence of “hypovitaminosis D,” defined more conservatively in their study as a serum 25-OH-D level of 12 ng/mL or below, as averaging 14% in a geographically diverse, healthy French population. Perhaps most compellingly, Gallacher et al.60 noted that 25-OH-D levels in elderly Scottish individuals with prior fractures averaged only 9.9 ng/mL; 91% of these subjects had levels below 20 ng/mL.

Clearly, nutritional vitamin D status is a serious problem around the world—and one that might be even worse when the levels used to determine “sufficiency,” “insufficiency,” and outright “deficiency” are further scrutinized.

**Optimal Levels of Circulating 25-Hydroxyvitamin D**

Levels of circulating 25-OH-D (calcidiol) that are below normal are problematic for bone health because they lead to decreased calcium absorption. What level of circulating 25-OH-D is necessary to optimize calcium absorption?

Heaney et al.54 compared intestinal calcium absorption at different levels of circulating 25-OH-D in 34 postmenopausal women. Patients with 25-OH-D levels of 34.6 ± 9.6 ng/mL absorbed 45% to 65% more calcium than patients whose 25-OH-D levels were 20.1 ± 6.3 ng/mL. This improvement was uniform with both calcium carbonate and citrate.

Impaired calcium absorption secondary to subtherapeutic 25-OH-D levels results in increased PTH secretion. This circulating PTH replenishes serum calcium at the expense of stores in bone by enhancing calcium liberation through bone catabolism.5 In the previously mentioned study of Irish women, Hill et al.58 showed a statistically significant inverse correlation between 25-OH-D and serum PTH, a finding that agrees with other analyses by Pasco61 and Holick.56 To ensure bone integrity, it is advisable to keep serum PTH levels low by maintaining sufficient levels of 25-OH-D. Reference 25-OH-D ranges indicative of sufficiency should be established to meet this goal.

Blood levels corresponding to adequacy and inadequacy vary according to the study and the investigators involved. Most studies were conducted under the assumption that the lower limit of normal for 25-OH-D was between 12 and 20 ng/mL.54,56,59,61,62–64

In 1995, Ooms et al.65 found that 12 ng/mL of 25-OH-D was sufficient to deter PTH elevations in a group of 330 elderly women; in other studies, however, the threshold value was much greater. Thomas63 observed that the statistical significance of the correlation between serum 25-OH-D levels and PTH in 290 hospital inpatients was lost at 25-OH-D levels above 15 ng/mL. That being said, absolute PTH levels were still lower in patients whose vitamin D levels were 20 to 30 ng/mL and above.

Both Chapuy60 and Holick56 found a negative correlation between PTH and 25-OH-D levels; PTH continued to decline until 25-OH-D levels reached 31 ng/mL and 29.8 ng/mL, respectively. Malabanan et al.66 determined that the level of maximal 25-OH-D effect was present at 20 ng/mL, but the low number of patients in that study (35) pale in comparison to the 3,000 enrolled by Chapuy and Holick.

In a study of more than 400 elderly patients by Dawson-Hughes et al.,67 the maximal suppressive effect of vitamin D on PTH continued up to a level of 44 ng/mL. Most profound were the results of Vieth and associates,68 who used mathematical modeling and data from more than 1,700 patients to determine that the inverse relationship between 25-OH-D levels and PTH could continue up to 25-OH-D concentrations as high as 67 ng/mL.

Although the exact point at which PTH levels are lowest in a given individual is probably subject to a number of factors, the studies reviewed here suggest that a desirable goal would be a level of 30 ng/mL of 25-OH-D or greater for the general population. The important question then becomes: at what amount of oral vitamin D supplementation do most people achieve this goal?

**Effect of Supplementation Oral Vitamin D on Circulating 25-Hydroxyvitamin D Levels**

Considerable research has been conducted on the dose dependence of oral vitamin D supplementation on serum 25-OH-D (calcidiol) levels. In light of the aforementioned serum 25-OH-D levels needed to maximally suppress PTH secretion, these findings cast doubt upon the ability of the
Adequate Intake (AI) for vitamin D to reliably achieve this goal: 400 IU in people 51 to 70 years of age and younger and 600 IU in those older than 70 years of age.

Much research concerning the effects of 400 IU of vitamin D daily has been conducted in older people. Ooms et al.\(^69\) found that this amount increased serum 25-OH-D levels from 10.8 to 24.8 ng/mL in a population with a mean age of 80.1 years. These results were remarkably similar to those obtained by Chel et al.\(^70\).

In a study of patients with a mean age of 75 years, Larsen et al.\(^71\) showed that 25-OH-D levels increased from 14.8 to 18.8 ng/mL after supplementation with 400 IU of vitamin D daily. It is unclear whether an additional 200 IU of vitamin D (to achieve 600 IU daily, according to current guidelines for this age group) would be sufficient to consistently increase serum 25-OH-D above a level of 30 ng/mL in these patients. However, because intestinal vitamin D absorption efficiency does not appear to decrease with age,\(^72\) a comparable patient younger than 50 years of age with baseline vitamin D levels such as those seen in these patient populations would be in danger of not achieving optimal 25-OH-D status with a daily supplement of oral vitamin D 400 IU.

Patel et al.,\(^73\) Tfelt-Hansen,\(^74\) and Hunter,\(^75\) showed studies of 400 IU, although patients' baseline levels also tended produced generally higher 25-OH-D levels than those seen in these patient populations. However, baseline 25-OH-D levels such as those seen in these patient populations would be in danger of not achieving optimal 25-OH-D status with a daily supplement of oral vitamin D 400 IU.

Peacock et al.\(^48\) assessed the impact of 600 IU of oral vitamin D daily on subsequent 25-OH-D levels. This dose was remarkably potent, boosting baseline 25-OH-D levels from 24.2 to 47 ng/mL in 75-year-old patients.

Studies conducted with 800 IU of vitamin D daily also produced generally higher 25-OH-D levels than those seen in studies of 400 IU, although patients’ baseline levels also tended to be higher. Patel,\(^73\) Tfelt-Hansen,\(^74\) and Hunter\(^75\) showed increases from 27.2 to 37.4 ng/mL, from 26.4 to 45 ng/mL, and from 28 to 42 ng/mL, respectively, in middle-aged women. Harris et al.\(^72\) found a uniform increase from 24 to 33 ng/mL in younger men (18 to 35 years of age) and in older men (62 to 79 years of age).

Barger-Lux et al.,\(^64\) in a mathematical calculation performed with data from 28-year-old men, predicted a remarkable increase from 26.8 to 64.4 ng/mL with 800 IU of oral vitamin D daily. Equally convincing were the results of earlier work done by Chapuy et al.,\(^59\) who documented increases of from 16 to 42 ng/mL when their population of 84-year-old women received 800 IU of vitamin D daily.

In summary, dosing of at least 800 IU of vitamin D would be far more likely than the current recommendations to consistently produce a desirable serum level of 25-OH-D and optimal PTH suppression in patients at various ages. Even at this level of dosing, it is conceivable that a subgroup of patients with very low 25-OH-D levels, such as the ones described earlier,\(^57\) would still not achieve vitamin D sufficiency by the newer threshold goals. In a study by Grados et al.,\(^76\) 800 IU of vitamin D improved a markedly deficient mean baseline value of 7 ng/mL to only 29 ng/mL.

### Oral Supplementation with Vitamins D\(_2\) and Vitamin D\(_3\)

Vitamin D\(_2\) (ergocalciferol) and vitamin D\(_3\) (cholecalciferol) are similar in structure but behave differently in humans in terms of their metabolic disposition and bioavailability.

When Trang et al.\(^77\) gave 72 patients 4,000 IU of either vitamin D\(_2\) or vitamin D\(_3\) daily for 14 days, the increase in serum levels of 25-OH-D was 70% greater in the vitamin D\(_2\) cohort. Similarly, Armas et al.\(^78\) found that a single oral dose of 50,000 IU of vitamin D\(_2\) given to 20 male volunteers produced serum 25-OH-D increases that peaked after only three days, whereas the equivalent dose of vitamin D\(_3\) produced a continual increase in 25-OH-D that peaked at two weeks. These two studies confirmed earlier work by Tjellesen et al.,\(^79\) who found that 4,000 IU of vitamin D\(_2\) did not produce the increase in total 25-OH-D seen with an equivalent dose of vitamin D\(_3\).

Aside from concerns over metabolic activity, Harris et al.\(^80\) showed that the bioavailability of equal doses of vitamin D\(_2\) was much greater in nine younger men (22 to 28 years of age) than in nine older men (65 to 73 years of age). This effect proved to be unique to vitamin D\(_2\) when the same authors conducted a similar study with vitamin D\(_3\) and saw no difference among the two age groups.\(^75\) For these reasons, oral vitamin D supplementation should consist of vitamin D\(_3\) (cholecalciferol) to ensure optimal absorption and a maximal serum 25-OH-D response. (Most references that publish vitamin D requirements state their recommendations in terms of vitamin D\(_3\) units.)

### Effects of Isolated Vitamin D Supplementation on Bone Mineral Density and Fracture Reduction

Assessments of vitamin D supplementation on BMD have produced variable results. Ooms et al.\(^69\) observed that 400 IU of vitamin D for two years improved BMD of the femoral neck in a group of 80-year-old patients. However, distal radius and femoral trochanter BMD did not significantly improve. Dawson-Hughes et al.\(^81\) showed that 400 IU of vitamin D for 12 months was able to attenuate BMD loss in a group of older women, an effect whose significance was driven by benefit seen in the late winter months.

In the Peacock study,\(^48\) no overall effect of 600 IU daily of vitamin D on BMD was observed in an elderly population. Patel et al.,\(^72\) assessing the effect of 800 IU daily for 12 months on 70 women (mean age, 47 years), found no significant benefit in any measure of BMD. These results were similar to the prior findings of Hunter et al.,\(^75\) who found that two years of vitamin D supplementation with 800 IU produced no benefit in BMD in 58-year-old women.

Baseline 25-OH-D levels may play a role in determining the BMD benefit associated with vitamin D supplementation. In the Peacock study, the subgroup of patients who consumed less than 720 mg of calcium daily at baseline did exhibit a statistically significant BMD benefit when compared with controls,\(^48\) an effect the authors were able to correlate with increasing 25-OH-D levels. The mild benefit seen in the Ooms study probably occurred through marked improvement of an outright baseline vitamin D deficiency.\(^69\) The lack of a statistically significant treatment effect in the Patel and Hunter studies might be a function of baseline 25-OH-D levels that, at 27.2 and 28 ng/mL, respectively, were already near the 30-ng/mL threshold.\(^73\)
Compelling evidence for the correlation between 25-OH-D status and BMD comes from a non-interventional study of more than 13,000 young patients in the U.S. by Bischoff-Ferrari et al. Conducting a regression analysis of the association between these two factors, these investigators found that in patients with a mean age of 32 to 35 years, BMD increased with increasing serum 25-OH-D levels up to 36 to 40 ng/mL. Within this range, one would have expected better results from the Patel and Hunter studies, which boosted 25-OH-D levels to 37.4 and 42 ng/mL, respectively. Possible reasons for a lack of BMD effect include Patel’s short study duration and Hunter’s baseline calcium intake, which was already near the Dietary Reference Intake (DRI).

For isolated vitamin D supplementation, the lack of a robust effect on BMD has translated to predictably varied results in the most important of all outcome measures—fracture prevention. Lips et al. could not prove a significant benefit of 400 IU of vitamin D in 2,600 elderly Dutch men and women, even with an increase in 25-OH-D levels from 10.8 ng/mL at baseline to almost 25 ng/mL. The study of 438 patients by Peacock, which demonstrated no BMD benefit with 600 IU of vitamin D supplementation, predictably showed no prevention in fracture frequency, even in the low-calcium subgroup. Meyer et al. also noted no fracture reduction with 400 IU of vitamin D daily in almost 1,200 nursing-home residents (average age, 85 years).

The only study with oral vitamin D supplementation unaccompanied by calcium to show a benefit in fracture incidence was conducted by Trivedi et al. In this study, 2,600 elderly British patients received 100,000 IU capsules of vitamin D every fourth month for five years. This average daily dose of just over 800 IU reduced the incidence of fractures at the hip, wrist, forearm, or vertebrae by an impressive one-third, compared with the rate for controls.

A possible explanation for the lack of a benefit in most of the patients studied might be related to calcium intake. In these four trials, mean calcium intakes were 870 mg, 650 mg, 450 mg, and 742 mg, respectively. The best of these values was roughly two-thirds of the DRI for calcium, a factor that might have inhibited the ability of vitamin D supplementation to enhance bone integrity.

More recently, a meta-analysis of randomized controlled trials compared the fracture-prevention capability of low doses of vitamin D at 400 IU/day with higher doses at 700 to 800 IU/day with varying degrees of calcium supplementation within the groups. In the 12 trials analyzed, the range of supplementation varied from nothing to 1,200 mg of calcium per day. Whereas the higher dose of vitamin D appeared to reduce the risk of hip and nonvertebral fractures in ambulatory or institutionalized elderly patients, the lower dose did not.

Despite the positive results with high-dose vitamin D in the ambulatory and institutionalized populations, a Cochrane review of more recent trials confirmed the vitamin’s benefit only in institutionalized patients. Once again, this review reiterated Bischoff-Ferrari’s contention that low-dose vitamin D was of no benefit in any population but that high-dose therapy benefited only institutionalized patients, lowering fracture risk by about 20%.

Of interest is the inextricably linked but independent mechanism whereby vitamin D might be able to reduce the risk of falling by improving a person’s muscle strength and neuromuscular function. Possibly by activating second messengers and phosphorylation, vitamin D seems to increase muscle protein synthesis. Supplemental vitamin D improves symptoms and function related to neurological manifestations of vitamin D deficiency, such as postural sway, rapid fatigue, psychomotor dysfunction, and difficulty climbing stairs or getting up from chairs.

Effect of Calcium plus Vitamin D on Bone Mineral Density and Fracture Risk

The final step in assessing the beneficial bone effects of calcium and vitamin D supplementation is to determine outcomes when the two are administered together. Grados et al. gave 192 women with a gross vitamin D deficiency (baseline 25-OH-D level of 7 ng/mL) 800 IU of vitamin D plus 1,200 mg of calcium daily for 12 months. The daily dietary calcium intake of these subjects was 700 mg. The treated group experienced significant lumbar, femoral, and whole-body BMD increases and a three-fold increase in 25-OH-D levels to 22 ng/mL.

A pair of studies by Chapuy, conducted in the early 1990s, echoed these results. In the earlier of the two studies, 1,700 elderly women with a 25-OH-D level of 16 ng/mL and a dietary calcium intake of just over 500 mg/day received 800 IU of vitamin D₃ and 1,200 mg of calcium daily for 18 months. BMD improved, and the incidence of fractures was emphatically reduced by 30% to 40%. These results were reproduced in 3,200 women over a 36-month period in the later study. Chapuy et al. then administered the same regimen to almost 600 women with baseline 25-OH-D levels of 8 to 9 ng/mL and a dietary calcium intake of 550 mg daily at the baseline evaluation. A 40% reduction in fracture risk was seen as 25-OH-D levels climbed to exceed 30 ng/mL.

Dawson-Hughes et al. conducted a study with 400 men and women with baseline 25-OH-D values of 33 ng/mL and a dietary calcium intake of 700 mg. They were given supplemental 700 IU of vitamin D and 500 mg of calcium daily for three years. Excellent BMD benefits and a significant reduction in fractures were noted.

Larsen et al. observed a 16% reduction in fracture risk with 400 IU and 1,000 mg of calcium daily in almost 5,000 patients with baseline 25-OH-D levels at about 15 ng/mL.

The findings of two trials seem to contradict this conclusion, but both have caveats. The Randomised Evaluation of Calcium Or vitamin D₃ (RECORD) trial tracked the fracture incidence in 1,300 patients who received 1,000 mg of calcium and 800 IU of vitamin D₃. No benefit was observed over a period of almost four years, even in patients with poor baseline calcium intakes and despite an increase in serum 25-OH-D from 15.2 to 25 ng/mL. It is worth noting that nearly half of the original enrollees were excluded on the basis of cognitive impairment; hence, the patients with highest risk of falls were excluded from the trial.

The Women’s Health Initiative tracked BMD and fracture rates in more than 18,000 women who received 1,000 mg of calcium and 400 IU of vitamin D₃ daily. No overall benefit was observed despite a mild 6% increase in BMD in the treated group.
participants. However, among the women who were at least 80% compliant with their treatment regimen, fracture risk was reduced in nearly 30%. This significant decrease was identical to that of patients who took no other form of calcium supplementation. Results did not vary according to baseline levels of 25-OH-D. That being said, serum levels were not reassessed after randomization to determine the effect of treatment with 400 IU of vitamin D.

From this group of studies, we can see that comprehensive supplementation with both calcium and vitamin D may have a synergistic effect in patients below benchmark intakes of either or both agents. Indeed, the results appear promising when these “deficient” individuals are able to achieve 25-OH-D levels near or above the proposed goal of 30 ng/mL.

Safety of Calcium and Vitamin D Supplementation

A major consideration in the advocacy of calcium and vitamin D supplementation as a public health policy is the measure of potential for risks compared with benefits. To date, safety analyses have shown that both agents are remarkably safe. In the dozens of trials involving some combination of calcium with or without vitamin D discussed in our article, only the Women’s Health Initiative showed a significant difference in kidney stone formation. Constipation is the predominant adverse effect seen with calcium supplementation; this factor may impair compliance, but it is generally not life-threatening.

Attempts to explore higher dosing ranges of vitamin D have been conducted infrequently because of concerns of toxicity, even though toxicity has been noted only rarely. In 1992, one paper reported a series of cases of hypervitaminosis D associated with milk consumption. However, the eight patients who experienced markedly elevated 25-OH-D concentrations might have been drinking milk that was erroneously fortified with more than 100,000 IU of vitamin D per glass, supplementation that is clearly excessive. Adams and Lee found that serum 25-OH-D levels in the range of 70 ng/mL caused hypercalcemia and hypercalciuria in a group of 40 people in Los Angeles, although this finding is aberrant when considered with other toxicity studies.

Heaney et al. applied aggressive dosing regimens to 67 Nebraskan men with baseline 25-OH-D levels of 26 to 28 ng/mL. The subjects were stratified to receive 1,000 IU; 2,000 IU; 5,000 IU; or 10,000 IU of vitamin D daily for 20 weeks during the winter. The men who received 1,000 IU showed an increase in 25-OH-D to only 33.6 ng/mL, the 2,000-IU group to 64.24 ng/mL, and the 10,000-IU group to 89.6 ng/mL. Serum calcium levels were carefully monitored in the two higher dosage groups, with no significant changes observed from baseline. From this trial, one could infer that the true upper level of the reference range was at least 90 ng/mL, although more trials are needed to establish safety at these chronic, elevated levels.

An apparent trend in vitamin D administration, mentioned in the Heaney study and in a study by Trang, is that serum 25-OH-D levels increase linearly with a given level of supplementation only to a certain point, at which time they achieve a plateau. This phenomenon, which may result from a relative decrease in liver hydroxylation with higher blood levels of vitamin D, should help to assuage fears of overt vitamin D intoxication, even with doses several times as large as the current Adequate Intake.

Current U.S. governmental recommendations advise against daily doses above 2,000 IU. This sentiment emerged after a study showed hypercalcemia in a handful of patients who had consumed 3,800 IU of vitamin D3 for three months. Vieth et al. sought to address the validity of this recommendation by giving 61 middle-aged men and women either 1,000 IU or 4,000 IU of vitamin D3 for two to five months, bringing serum 25-OH-D levels from 16.4 ng/mL at baseline to 27.5 ng/mL and 38.6 ng/mL in the two cohorts, respectively. The investigators noted no significant increases in serum calcium or urinary calcium excretion during the dosing period.

In summary, calcium and vitamin D supplementation appear to be safe for most people. We recommend periodic laboratory monitoring of serum calcium and phosphorus levels in patients whose calcium supplementation, with or without vitamin D, is higher than the values recommended. Because laboratory monitoring of these values is a routine practice among primary care practitioners, it should add no appreciable cost to the health care system.

Recommendations for Calcium and Vitamin D Supplementation

Osteoporosis increases in prevalence with advancement in age, and the average age of the population in the U.S. is indeed steadily increasing. The costs to our medical system have been substantial to date and only stand to grow in the future. For these reasons, cost-effective therapeutic options today that can prevent or ameliorate the manifestations of this disease state would impart a public health benefit of significant proportions in the future. Table 3 summarizes our recommendations.

In terms of calcium supplementation, to ensure maximal absorption and utilization of an ingested dose, calcium citrate may be preferable to calcium carbonate, especially in individuals with achlorhydria or those who are taking potent acid-lowering drugs such as PPIs. Optimal timing of calcium supplementation has been studied, but results are inconclusive.

Contrary to popular belief, once-daily dosing of the entire DRI of calcium, especially in the evening, may provide benefits that are at least equal to those of divided doses, although this option has not proved definitive. For this reason, as we recognize the need to foster daily compliance for calcium intake, we recommend at least twice-daily divided doses of calcium sufficient to meet the current DRI for each age group.

As demonstrated by numerous studies showing disturbingly low levels of serum 25-OH-D in a vast array of populations, vitamin D deficiency is a public health problem. Supplementation with oral vitamin D3 can be more effective than with vitamin D2; the latter is less reliably absorbed and has a less robust effect on serum 25-OH-D levels.

As for dosage, the effect of daily supplementation with 400 IU of vitamin D on serum 25-OH-D levels, BMD, and the incidence of fractures has proved to be largely inadequate. Dosing with 600 IU of vitamin D daily seems to provide a better
Utilization of Calcium and Vitamin D

Vitamin D may reduce the risk of falls by improving neuromuscular function, thereby enhancing utilization of calcium, vitamin D may provide an advantage by improving neuromuscular function, thereby decreasing the risk of falls.

The old standard of 400 to 600 IU/day seems inadequate, which may be improved by combining with 2,000 to 4,000 IU/day. Vitamin D 3 (cholecalciferol) is preferred to vitamin D2 (ergocalciferol).

Table 3 Summary of “Pearls” Toward Optimal Utilization of Calcium and Vitamin D

**Calcium screening and assessment may be done with baseline and serial 25-hydroxyvitamin D levels:**

- Calcidiol (25-OH-D) levels are of benefit in screening for at-risk patients. Levels below 20 ng/mL imply “insufficiency” of vitamin D.
- Calcium with vitamin D therapy should be started to achieve a level of at least 30 ng/mL (but not greater than 60 ng/mL) so that calcium utilization is optimized.

**Barring clinical contraindications, calcium along with vitamin D should be given to all “at-risk” individuals:**

- All patients taking antiresorptive or osteoblast stimulant therapies so that a substrate is provided to optimize benefit.
- Patients unable to obtain, afford, or tolerate antiresorptive agents or osteoblast stimulants may still benefit from taking calcium with vitamin D.

**Calcium product:**

- The citrate salt shows improved absorption characteristics over the carbonate salt, but the carbonate form may suffice if citrate is too costly or unavailable.
- Calcium citrate is preferred for patients taking potent acid-lowering agents (e.g., proton pump inhibitors), but carbonate may be acceptable if it is always taken with food.
- Patients with end-stage renal disease should avoid calcium citrate because of increased aluminum absorption, but carbonate and acetate salts are safe.

**Calcium dose:**

- Doses need not exceed 1 to 1.5 g of elemental calcium per day. If vitamin D supplementation is optimized, even lower doses benefit.
- To ensure compliance, twice-daily dosing is preferred to three times daily.
- Even though the carbonate salt is best given in amounts not exceeding 500 mg per dose because of dose-dependent absorption, citrate salt absorption may not be limited by this threshold.

**Vitamin D product and dose:**

- Vitamin D3 (cholecalciferol) is preferred to vitamin D2 (ergocalciferol).
- The old standard of 400 to 600 IU/day seems inadequate, especially in the elderly. At least 800 IU/day and probably 1,000 to 1,200 IU/day seem more likely to achieve the desired target 25-OH-D level above 30 ng/mL.
- A daily multivitamin infusion with 400 IU, plus a combination calcium/vitamin D product, should suffice to achieve the desired daily dose of vitamin D, but extra vitamin D tablets may be added at minimal cost.
- Vitamin D may reduce the risk of falls by improving muscle strength.

**REFERENCES**


33. Guilmant J, Guilmant S. Comparison of the suppressive effect of two doses (500 mg vs. 1500 mg) of oral calcium on parathyroid hormone secretion and on urinary cyclic AMP. Calcif Tiss Int 1993;53(5):304–308.


41. Levis S, Gomez A, Jimenez C, et al. Vitamin D deficiency and osteoporosis: The influence of calcium intake and vitamin D inadequacy in Scottish adults with non-vertebral fra-


Continuing Education Questions for Physicians and Pharmacists

**P&T® 2007;32(9):502–513**  
APCE Program # 079-000-07-021-H04-P  
Expiration Date: September 30, 2008

**Topic: Calcium and Vitamin D in the Prevention and Treatment of Osteoporosis:**  
Shedding Light on New Developments

**CME Accreditation**

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Jefferson Medical College and MediMedia USA, Inc.

Jefferson Medical College of Thomas Jefferson University, as a member of the Consortium for Academic Continuing Medical Education, is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. All faculty/authors participating in continuing medical education activities sponsored by Jefferson Medical College are expected to disclose to the activity audience any real or apparent conflict(s) of interest related to the content of their article(s). Full disclosure of these relationships appears on the last page of the article.

**Continuing Medical Education Credit**

This CME activity is designed to assist physicians and other health care professionals who are P&T committee members in making formulary decisions. Its goal is to increase participants’ ability to recognize and treat important medical problems.

Jefferson Medical College designates this continuing medical education activity for a maximum of one Category 1 credit toward the Physician’s Recognition Award (PRA) of the American Medical Association. Each physician should claim only those credits that he/she actually spent in the educational activity.

This credit is available for the period of one year from the date of publication.

Although forms will be processed when received, certificates for CME credits will be issued every six months, in February and August. Interim requests for certificates can be made by contacting the Jefferson Office of Continuing Medical Education at (215) 955-6992 or by going online to http://jeffline.tju.edu/jeffcme/.

**Continuing Pharmacy Education Credit**

The Department of Health Policy, Thomas Jefferson University Hospital, is approved by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education and complies with the Criteria for Quality for continuing pharmacy education programming. This program (079-000-07-021-H04-P) is acceptable for 1.0 hour of continuing education credit (0.1 CEUs) in states that recognize ACPE-approved providers. Statements of Credit indicating hours/CEUs will be mailed within six to eight weeks to participants who completed this activity and submitted a completed evaluation with payment.

**How to Apply for CE Credit**

1. Each CE article is prefaced by learning objectives for participants to use to determine whether the article relates to their individual learning needs.
2. Read the article carefully, paying particular attention to the tables and other illustrative materials.
3. Complete the questions and fill in the answers on the evaluation form on the next page.
4. Complete the CE Registration and Evaluation Form. Type or print your full name and address in the space provided, and evaluate the activity as requested. In order for the form to be processed, all information must be complete and legible.
5. Payment of $10 per exam is required for processing and maintenance of records. Make checks payable to P&T®. This processing fee is non-refundable.
6. Send the completed form, answer sheet, and $10 payment to:  
   Department of Health Policy  
   Thomas Jefferson University  
   Attn:  Continuing Education Credit  
   1015 Walnut Street, Suite 115  
   Philadelphia, PA 19107
7. Be sure to mail the Registration, Evaluation Form, and $10 payment within one year of the date of publication. After that date, this article will no longer be designated for credit and forms cannot be processed.
Continuing Education Questions for Physicians and Pharmacists

TOPIC: Calcium and Vitamin D in the Prevention and Treatment of Osteoporosis: Shedding Light on New Developments
APCE Program # 079-000-07-021-H04-P

CE Evaluation: Select the one best answer to each of the following questions, and record your response on the examination answer sheet. Complete the additional requested information. Forward the answer sheet, with appropriate payment, to the Department of Health Policy, Thomas Jefferson University Hospital, at the address indicated. A certificate of completion will be mailed within six to eight weeks of receipt of your exam/payment. (A minimum test score of 70% is required.)

Multiple Choice
Select the one correct answer.

1. Which of the following over-the-counter formulations is most likely to display dose-dependent absorption?
   a. calcium citrate
   b. calcium carbonate
   c. calcium gluconate
   d. calcium chloride

2. Based on the studies reviewed by the authors, which statement (or statements) is true?
   a. Vitamin D deficiency is very common.
   b. Vitamin D in combination with calcium may have a synergistic effect in patients.
   c. Vitamin D may reduce the risk of falls through improvements in muscle strength and neuromuscular function.
   d. all of the above

3. As mentioned in the article, which of the following is the best over-the-counter option for calcium supplementation for a patient who is also on long-term proton pump inhibitor therapy?
   a. calcium gluconate
   b. calcium citrate
   c. calcium carbonate
   d. calcium bromide

4. Intestinal vitamin D₃ absorption efficiency does not appear to decrease with age:
   a. True
   b. False

5. Calcium and vitamin D supplementation:
   a. appears to be decidedly safe for the general population.
   b. should not be monitored in patients who supplement at higher doses of calcium and/or vitamin D than those currently recommended.
   c. does not result in constipation as the predominant adverse effect seen with calcium.
   d. is not an option in the prevention and treatment of osteoporosis.

6. The absorption of calcium occurs predominantly via which mechanism in the gastrointestinal tract?
   a. inactive transport
   b. passive transport
   c. active transport
   d. paracellular transport

7. According to the article, what is the minimum desirable goal blood level of 25-hydroxyvitamin D (25-OH-D) for the general population?
   a. 30 ng/mL
   b. 15 ng/mL
   c. 5–10 ng/mL
   d. 40–45 ng/mL

8. Adequate intake of vitamin D to achieve goal blood levels of 25-OH-D levels:
   a. does not maximally suppress parathyroid hormone secretion.
   b. can be achieved with 400 IU of vitamin D.
   c. always results in vitamin D “sufficiency” in patients with very low 25-OH-D levels.
   d. may be more likely to occur at doses of at least 800 IU of vitamin D.

9. Which of the following is the active form of vitamin D that is the primary control of calcium homeostasis?
   a. calcidiol: 25(OH)D
   b. calcitriol: 1,25(OH)₂D
   c. cholecalciferol
   d. 24,25(OH)₂D

10. According to the current evidence, isolated vitamin D supplementation at doses of less than 800 IU does not provide reliable bone mineral density improvement or reduced fracture risk:
    a. True
    b. False
CE Registration and Evaluation Form

Date of publication: September 2007
Title: Calcium and Vitamin D in the Prevention and Treatment of Osteoporosis: Shedding Light on New Developments
Authors: Ian B. Hollis, PharmD, BCPS, and Randolph Regal, BS, PharmD
Submission deadline: September 30, 2008
APCE Program # 079-000-07-021-H04-P

Registration
Name: ____________________________________________________________ Degree: ____________________________________
Street address: ______________________________________________  Last 4 Digits of Social Security No. (Web ID): __________
City: ___________________________________  State: _________  Zip:__________  Telephone:  _____________________________
E-mail Address: _______________________________________   Check one:
I   I   I   I  Physician  I   I   I  Pharmacist  I   I   I  Other
Time needed to complete this CE activity in hours:  I   I   I  0.5 hr  I   I   I  1 hr  I   I   I  1.5 hr  I   I   I  2 hr  I   I   I  Other _________________________
Certification: I attest to having completed this CE activity. ___________________________________________________________  Signature (required) Date _______________

Answer Sheet
Please fill in the box next to the letter corresponding to the correct answer

1.   a □ b □ c □ d □   6. a □ b □ c □ d □
2. a □ b □ c □ d □   7. a □ b □ c □ d □
3. a □ b □ c □ d □   8. a □ b □ c □ d □
4. a □ b □ c □ d □   9. a □ b □ c □ d □
5. a □ b □ c □ d □   10. a □ b □ c □ d □

Evaluation
Rate the extent to which:

<table>
<thead>
<tr>
<th></th>
<th>Very High</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
<th>Very Low</th>
</tr>
</thead>
</table>
1. Objectives of this activity were met |           |      |          |     |          |
2. You were satisfied with the overall quality of this activity |           |      |          |     |          |
3. Content was relevant to your practice needs |           |      |          |     |          |
4. Participation in this activity changed your knowledge/attitudes |           |      |          |     |          |
5. You will make a change in your practice as a result of participation in this activity |           |      |          |     |          |
6. This activity presented scientifically rigorous, unbiased, and balanced information |           |      |          |     |          |
7. Individual presentations were free of commercial bias |           |      |          |     |          |
8. Adequate time was available for Q&A |           |      |          |     |          |
9. Which ONE of the following best describes the impact of this activity on your performance:
   □ This program will not change my behavior because my current practice is consistent with what was taught.
   □ This activity will not change my behavior because I do not agree with the information presented.
   □ I need more information before I can change my practice behavior.
   □ I will immediately implement the information into my practice.
10. Will you take any of the following actions as a result of participating in this educational activity (check all that apply)
   □ Discuss new information with other professionals
   □ Consult the literature
   □ Discuss with industry representative(s)
   □ Participate in another educational activity
   □ Other ____________________________

Send the completed form and $10 payment (make checks payable to P&T) to: Department of Health Policy, Thomas Jefferson University, Attn: Continuing Education Credit, 1015 Walnut Street, Suite 115, Philadelphia, PA 19107.