Calcium and Vitamin D Supplementation Update for the Prevention and Treatment of Osteoporosis

Kimberly A.B. Cauthon, Assistant Professor, and Shannon Li, PharmD Candidate Midwestern University College of Pharmacy-Glendale. The authors have no financial relationships to disclose.

Universal Activity # 0143-9999-11-009-H01-P
1.5 Credit Hours (0.15 CEUs)

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Goal
The goals of this home-study CPE activity are to:
● Review and update pharmacists with the most current information on the recommended doses of calcium and vitamin D supplementation for osteoporosis prevention and treatment;
● Present information that examines the relationship between calcium, vitamin D, and cardiovascular health.

Objectives
At the conclusion of this knowledge-based lesson, successful participants should be able to:
1. Recall the basic physiologic roles of calcium and vitamin D.
2. Identify appropriate calcium and vitamin D supplementation dietary reference intakes and new tolerable upper limits set by the Institute of Medicine (IOM) for osteoporosis prevention and treatment.
3. Discuss recent information investigating the risks of calcium/vitamin D on cardiovascular health.
4. Compare and contrast the different types of calcium and vitamin D supplements and dosing strategies.
5. Develop effective counseling strategies for calcium and vitamin D use, dosing, and adverse effects.

Introduction
Hippocrates (460 BC – 370 BC) was known as the Father of Western Medicine and one of his most notable works was the Hippocratic Oath that health care professionals still abide by to this day. The oath includes the promise "to abstain from doing harm" and to treat the patient only if the benefit outweighs the risk.[1] Pharmacists are constantly at the frontlines of balancing the beneficial and harmful effects of medications and supplements for patients.

Conflicting information for calcium and vitamin D has been reported that makes it unclear for pharmacists whether calcium and vitamin D supplements are preventing harm by decreasing osteoporosis, falls, and fractures or causing harm by increasing the risk of cardiovascular events. The evidence for how efficacious they are in preventing falls and fractures continues to be debated but it is largely accepted that they are important for their beneficial effects on bone density.[2-9] Osteoporosis is a major health concern in the elderly population and heart disease continues to be the leading cause of death in men and women.[10] One in three persons sixty-five years and older will fall once this year and twenty to thirty percent of those falls will result in moderate to severe injury, such as fracture.[11,12] One in five patients with hip fracture will die within a year of their injury; therefore appropriate osteoporosis prevention and treatment is of immense importance.[12,13]

The appropriate amounts of calcium and vitamin D continue to be examined and questioned. The Institute of Medicine (IOM) released a new report on the Dietary Reference Intakes (DRI's) for calcium and vitamin D on November 30, 2010 and has decreased the calcium upper limit from its previous report.[14] There is also conflicting information on the proper form of vitamin D and when a vitamin D level is important to obtain.[14-16] The calcium and vitamin D information presented in this continuing education program addresses the physiologic roles, IOM report, dietary supplementation, cardiovascular effects, treatment doses, guideline review, and counseling parameters.

Physiologic Role of Calcium
Calcium is an essential inorganic electrolyte that is found mostly in the bones and teeth.[17] Calcium is critical for mediating vascular contraction and

vasodilation, muscle function, nerve transmission, intracellular signaling, and hormonal secretion. Since 99% of the body's calcium is found as calcium hydroxyapatite ($Ca_{10}[Pa_4]_6[OH]_2$) in bones and teeth, the need for calcium is determined by the skeletal requirements.

Calcium is constantly being lost and replenished in the bones and it is essential that the replenishment of supply outweighs the amount being lost. In different stages of life, the amount of bone formation and resorption changes and therefore calcium intake recommendations are dependent upon age. Up until the age of 25, bone formation is still dominant over bone resorption. After an adult reaches 25 years of age, the peak bone mass has been achieved as the rate of bone formation and resorption are at an equilibrium. In older adults, bone resorption exceeds bone formation. When a woman goes through menopause, the drop in estrogen is considered the predominant factor for accelerated bone loss.[8,18]

Calcium balance in the body is determined by absorption from the intestines, storage in the bones, and elimination or reabsorption from the kidneys. It is absorbed mostly in the duodenum and proximal jejunum of the small intestine and is dependent on vitamin D and its activation by parathyroid hormone (PTH). Calcium is not arbitrarily absorbed from the intestines and a majority is lost in the feces. An acidic intestinal pH is usually necessary for ionization of calcium and ionized calcium is the form of calcium that is absorbed.

Decreased ionized calcium in the blood circulation will increase PTH synthesis and release. PTH will work immediately to increase the circulation of calcium by promoting the movement of calcium from the bone to the plasma. PTH influences the reabsorption of calcium from the kidney's distal tubule and indirectly increases intestinal absorption by stimulation of vitamin D synthesis. By inducing bone resorption to maintain calcium serum levels, this decreases the skeletal mass. Normal total serum calcium ranges from 8.5 to 10.5 mg/dL. Calcium is transported in the blood bound to albumin, complexed with sulfate, phosphate, or citrate or in a free ionized state. The serum calcium does not reflect the bone content of calcium; therefore the serum calcium is not routinely checked during calcium supplementation for osteoporosis treatment and prevention. The calcium level is unlikely to be elevated due to the protective mechanisms in place unless the patient has poor renal function.[17,19] The serum calcium level should be checked on initial exam for osteoporosis. If the calcium is high, it could indicate hyperparathyroidism and if it is low indicates vitamin D deficiency or gastrointestinal malabsorption.

Calcium intake is important in all states of life but the focus of this paper is on the middle-aged and elderly as their balance of bone formation and destruction is compromised. As a person ages, the calcium intestinal absorption is decreased and the renal tubular re-absorption is decreased. Common reasons for calcium deficiency in the bones include poor calcium intake, poor intestinal absorption, and vitamin D deficiency.[8]

Adequate amounts of calcium are recommended in all osteoporosis treatment and prevention guidelines because of calcium's physiologic role as the bone building block but it is still being studied due to lack of information on its efficacy alone for fall and fracture outcomes. Most studies have looked at the combination of calcium and vitamin D together but in general it is thought that calcium has a modest effect on preventing osteoporotic fractures.[7]

Physiologic Role of Vitamin D

Vitamin D is a fat-soluble vitamin and a steroid hormone that is necessary for calcium to be absorbed and plays an important role in bone health. Vitamin D is involved in neuromuscular function, the immune system, and multiple other body systems. It has been actively researched in the last few years regarding its potential benefits other than bone health. Emerging research has shown a reduced risk for type 1 diabetes, some cancers, autoimmune diseases, and infectious diseases with vitamin D supplementation.[9,20]

There are generally considered to be two ways the body can acquire Vitamin D. It can be made endogenously through ultra-violet rays from sun exposure or through consumption of Vitamin D rich foods or supplements. Vitamin D_3 (cholecalciferol) is produced from the conversion of 7-dehydrocholesterol in the epidermis and dermis in humans by UV rays, and vitamin D_2 (ergocalciferol) is produced in mushrooms, yeast, and plants. Usually, cholecalciferol in the diet is from animal sources and ergocalciferol is from plant sources. The chemical difference between

vitamin D_2 and D_3 is in the side chain. In contrast to vitamin D_3, vitamin D_2 has a double bond between carbons 22 and 23 and a methyl group on carbon 24.[9,17,19]

Vitamin D_2 and D_3 must undergo a set of two hydroxylations in order to become the active form. The first addition of a hydroxyl group occurs in the liver and converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. Calcidiol is the transport and storage form of vitamin D in the blood circulation and mirrors the amount stored in muscles and fat. The second addition of a hydroxyl group occurs in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], also known as calcitriol. The enzyme 25-hydroxyvitamin D_3 1-alpha-hydroxylase is responsible for the conversion of calcidiol to calcitriol in the kidneys. PTH controls the release of this enzyme depending on whether calcium and phosphate levels are low in the blood circulation. When the body senses low serum calcium levels, it will increase the production of 25-hydroxyvitamin D_3 1-alpha-hydroxlase and therefore, more calcitriol (the active form of vitamin D) will be produced. Calcitriol will increase the uptake of calcium from the gastrointestinal tract into the blood, decrease the transfer of calcium from blood to the urine by the kidney, decrease PTH production, and increase the release of calcium into the blood from bone. Calcitriol promotes intestinal calcium absorption by increasing the expression of epithelial calcium channel protein which increases transport of calcium across the membrane.[17,19, 21]

It might seem counterintuitive that the same hormone that causes an increase in serum calcium levels could also lead to demineralization of bone. However, calcitriol indirectly affects bone mineralization by causing demineralization of bone only when serum calcium concentrations fall below the range level needed for normal bodily functions. It is an emergency mechanism in order to use the stores of calcium in bones but only when necessary.

Adequate amounts of vitamin D are recommended in all osteoporosis treatment and prevention guidelines due to its overall role in increasing calcium concentrations.

IOM Recommended Daily Allowances for Calcium and Vitamin D

The IOM new dietary reference intakes for calcium and vitamin D were released in 2010 and are presented in Table 1.[22] The IOM used bone health as the basis for their recommendations on dietary reference intakes with the goal to serve as a guide for good nutrition. The new IOM report was requested by the United States and Canadian government to assess the current data and provide an update from the 1997 report for recommended intakes and disease state indicators.

The report provides recommendations on calcium and vitamin D estimated average requirements, recommended dietary allowances, and tolerable upper intake levels. The amount of vitamin D recommended was based on the assumption of minimal sun exposure. Estimated average requirements (EAR) reflect the estimated median requirement or the adequate amount for 50% of individuals. EAR is commonly used for planning and assessing intakes for groups of people such as elementary school meals or the nutrition label. The EAR for calcium for adults 31 to 50 years of age and males up to 70 years of age is 800 mg day and is increased to 1,000 mg per day for all adults greater than 70 years of age and females between 51 to 70 years of age. The EAR for vitamin D is 400 IU per day in all persons 31 years of age and older. Recommended dietary allowance (RDA) is derived from the EAR and meets or exceeds the requirement for 97.5% of the healthy population. This is usually seen as the goal for dietary intake by healthy people. RDA is the amount that should decrease the risk of osteoporosis but does not necessarily replace calcium and vitamin D if the patient has a condition that causes inadequate absorption. It also does not mean that it is the amount needed if the patient already has the disease state from lack of that nutrient, such as osteoporosis. The calcium RDA is 1,000 mg daily for adults 31 to 50 years of age and males up to 70 years of age and changes to 1,200 mg daily for females 51 to 70 years of age and all persons greater than 70 years of age. The vitamin D RDA is 600 IU daily for all adults 31 to 70 years of age and 800 IU daily for all adults greater than 70 years of age. Tolerable Upper Intake Level (UL) means that if the intake increases above the UL, the risk of adverse effects increases. The UL is the highest average daily intake that is not likely to pose risk of adverse effects in almost all individuals in the general population. For calcium, the UL is 2,500 mg daily for

adults ages 31 to 50 years and 2,000 mg for all persons 51 years of age and older. For vitamin D, the UL is 4,000 IU for all persons ages 31 and older.[2,22,23]

Some of the changes from the 1997 report include that the UL for calcium for all adults 51 years of age and older has decreased to 2000 mg per day compared to 2,500 mg per day.[24] The IOM report states that postmenopausal women may be getting too much calcium, thereby increasing their risk of kidney stones. The vitamin D amounts for the RDA and UL increased from the 1997 report. The IOM reports that the population vitamin D intake is below their stated requirement yet the general population blood levels of vitamin D are above goal. Therefore, the IOM conclusion is that vitamin D acquired from sunlight might be playing an important role in the synthesis of vitamin D in Americans.

For many of the questions the IOM set out to answer, the conclusions were that more information was needed before a recommendation could be made. Outcomes related to chronic disease indicators such as cardiovascular disease could not be linked reliably with calcium or vitamin D intake and were often conflicting. The following were also identified as uncertainties in the report: the tendency for study protocols to administer a combination of calcium and vitamin D so that each nutrient could not be assessed independently; that individuals who experience sun exposure might have a more uncertain dietary requirement greater than for those who do not; the lack of clarity concerning the validity of the serum 25(OH)D measure as a biomarker and the variability surrounding measures of serum 25(OH)D concentrations owing to different laboratory methodologies. The serum 25(OH)D cut-points defined as indicative of deficiency for vitamin D have not undergone a systematic, evidence-based review. This was of concern due to the classification of 25(OH)D levels greater than 50 nmol/L (20 ng/ml) as being deficient and patients are being treated with vitamin D doses which are much higher than the amount recommended by the IOM report.[25]

Calcium and Vitamin D Dietary and non-supplement Sources and Recommendations

Adults in the United States consume, on average, 600 to 700 mg of calcium per day in their dietary intake.[26] Calcium is found in dairy products, fruits, vegetables, and grain products. Approximately 75% to 80% of calcium in the diet is from dairy products. Patients should be advised to increase their dietary calcium consumption through calcium rich foods or calcium fortified products before taking supplements to meet their RDA. However, increased consumption of dairy products could lead to increased intake of saturated fat as well. Therefore, a variety of calcium rich foods should be recommended in order to maintain a heart healthy diet while obtaining the necessary calcium needed.[8,25]

Patients should be made aware of the RDA and advised to keep track of how much calcium they are ingesting daily to determine if they are meeting their RDA. An easy calculation to estimate daily calcium intake is to multiply the number of the following servings by 300 mg and add them together: 8 ounces of milk or yogurt or 1 ounce of cheese and multiply the number of the following servings by 150 mg: 4 ounces of cottage cheese or ice cream.[27] Calcium may be poorly absorbed with certain vegetables that have the acids of oxalates that bind to the calcium. Examples of vegetables with these acids are spinach, collard greens, sweet potatoes, rhubarb, and beans. For more detailed amounts of foods high in calcium, refer to Table 2. There are several calcium calculator websites. One example is the International Osteoporosis Foundation (IOF) website, which is based on the World Health Organization calcium intake recommendations at http://www.iofbonehealth.org/patients-public/calcium-calculator.html.

Adults can get vitamin D_3 activation from the sun UVB rays or can ingest Vitamin D in their diet. Cloud cover reduces UV rays by 50% and any sunscreen with a sun protection factor (SPF) greater than eight will prevent the production of vitamin D_3. UVB radiation also does not penetrate glass, therefore sun exposure through a window or car door will not allow for vitamin D_3 formation. Despite the body's natural mechanism of vitamin D production, the American Academy of Dermatology does not recommend that vitamin D should be obtained from unprotected exposure to UVB radiation.[28] Their position statement includes that there is no scientifically validated, safe threshold level of UV exposure from the sun that allows for maximal vitamin D synthesis without increasing the skin cancer risk. In addition, as a person gets older, the body becomes less efficient at

producing vitamin D from sunlight. Dietary intake for the elderly population is more important, especially those in a nursing home or who reside mostly indoors. Other factors that affect vitamin D activation by the sun include geographic location, time of day, darker skin tones, and the calendar season.[9]

Adults in the United States consume approximately 200 IU of Vitamin D a day from their diet.[26] Natural food sources of Vitamin D are limited and include the flesh of certain fishes such as mackerel, salmon, and tuna. Small amounts of vitamin D are found in fish liver oils, mushrooms, egg yolks, beef liver and cheese. Due to this small selection of natural Vitamin D in foods, Americans obtain most of their Vitamin D from fortified foods such as milk, cereal and calcium fortified juices/drinks. D_2 is used to fortify milk and cereals.[29,30] An easy calculation to estimate vitamin D intake is to multiply every eight ounce serving of milk by 100 to estimate the IU per day.[27] For more detailed dietary vitamin D information, refer to Table 3.

Calcium and Vitamin D and Cardiovascular Risk

A lot of talk has been buzzing around the meta-analysis by Bolland et al. published in 2010, suggesting that calcium supplementation may increase the risk of heart attacks.[31] Concern has been raised if patients should continue their calcium supplements. Previous studies have been conducted that showed calcium had slight benefit in decreasing blood pressure and calcium is a component of the recommended hypertension treatment diet.[8] The Dietary Approaches to Stop Hypertension (DASH) diet recommends two to three servings of low fat milk and milk products daily for a 2,000 calorie diet.[32] High dietary intake of calcium was associated with less heart disease mortality in the Iowa Women's Health Study.[33] There have been no randomized, double-blind, placebo controlled trials that have studied calcium supplements with the primary endpoint of cardiovascular events so Bolland and authors conducted this meta-analysis.

The meta-analysis goal was to examine cardiovascular events in randomized trials with calcium supplements. The studies included were double blind, placebo-controlled trials with doses of calcium supplements ≥ 500 mg/day in patients over 40 years of age. The studies also had to have enrolled 100 or more patients and had to have lasted for greater than one year. Trials were excluded if vitamin D was given to the calcium group and not the placebo group, if calcium was given by diet only, and if the patients had major disease states other than osteoporosis. The primary end points for the meta-analysis were time to first myocardial infarction, time to first stroke, and time to first event for the composite end point of myocardial infarction, stroke, or sudden death. The secondary endpoint was time to death (all-cause mortality).

Two analyses were conducted within the meta-analysis: one for studies with trial level data and one for studies with patient level data analysis. Eleven studies with almost 12,000 participants were analyzed with the trial level data. There were 166 myocardial infarctions in the calcium group versus 130 in the placebo group. The risk of myocardial infarction was found to be higher in the calcium group (HR 1.27, 95% CI 1.01 to 1.59, p=0.038). Five studies with the patient level data included over 8,000 patients. There were 143 myocardial infarctions in the calcium group versus 111 in the placebo group. The risk of myocardial infarction was found to be higher in the calcium group (HR 1.31, 95% CI 1.02 to 1.67, p=0.035). The study suggests those patients who take more than the median dietary intake of calcium without vitamin D supplementation, have a 30% increased risk of myocardial infarction. The average dose of calcium supplements was 1,000 mg daily. There was not a statistical difference between groups for stroke, the composite endpoint, or death but the numbers were increased in the calcium group. The authors proposed that treatment of 1,000 people with calcium for five years would cause an additional fourteen myocardial infarctions and prevent twenty-six fractures. Limitations of the meta-analysis were that none of the studies used were designed to primarily examine the link of cardiovascular disease and calcium supplements. The meta-analysis authors counted events rather than the number of people with events.

Wang et al. published a systematic review on vitamin D and calcium supplementation in prevention of cardiovascular events shortly after the previous meta-analysis.[34] The goal of the review was to assess if vitamin D, calcium, or the combination reduced the risk of cardiovascular events. They included seventeen prospective cohorts or randomized controlled trials that reported cardiovascular events. Four were specifically randomized trials for calcium supplementation alone and there were more cardiovascular events reported in

the calcium group but none had statistical significance. This could have been due to the low number of participants and power was not met. The systematic review's conclusion was that there was limited data. From the limited data, vitamin D supplements may reduce cardiovascular events and calcium has little effect on events.

The mechanism for the increase in myocardial infarctions is unclear but it is proposed that calcium is found in atherosclerotic lesions and also contributes to vessel calcification. Manson et al. conducted a study that measured coronary artery calcium nested within the Women's Health Initiative (WHI) trial.[35] The study sample size was 754 women ages 50 to 59. The two groups were a placebo compared to calcium/vitamin D 1,000 mg/400 IU daily. There was no statistical difference in coronary artery calcium scores between the groups. Previous studies, such as the WHI calcium-vitamin D randomized controlled trial showed that vitamin D might be used as a supplement to counteract the potential cardiac risk seen with patients taking only calcium or showed no difference.[36-38]

As with calcium, there have been no randomized trials that have studied a primary endpoint of cardiovascular events with vitamin D supplementation. Pittas et al. conducted and published a meta-analysis in 2010 that looked at vitamin D supplementation and blood pressure lowering did not find a significant decrease in the systolic or diastolic blood pressure.[39] The International Osteoporosis Foundation (IOF) briefly mentions that vitamin D deficiency has been implicated as a contributing factor to cardiovascular disease but there is not enough information at this time to make a definitive link.[15] Observational studies have demonstrated that low 25(OH)D levels are associated with cardiovascular events.[40,41] Pittas et al. reported there was no decrease in cardiovascular risks after increasing the 25(OH)D level.

More randomized, controlled trials are recommended to establish these relationships along with the best vitamin D dose and 25(OH)D levels.[42] A current, prospective, randomized trial is the Vitamin D and Omega-3 Trial (VITAL) that is currently enrolling 20,000 participants in the United States. The study groups are a combination of vitamin D and fish oil, vitamin D only, fish oil only, or placebo. The participants will be followed for cardiovascular events and other disease states. The website is www.vitalstudy.org.

At this time, it would be best to counsel patients to obtain as much of the RDA calcium from their diet and not surpass the recommended UL as there is no evidence that dietary calcium increases cardiovascular events. Recommend calcium supplements only if the dietary calcium does not meet the RDA. Continue to recommend vitamin D supplementation based on the IOM recommendations.

Calcium Supplement Treatment Doses, Guideline Recommendations, and Counseling Points

The calcium dose that is most effective for osteoporosis prevention has been stated by IOM, but the dose needed for fall and fracture prevention in patients with osteoporosis or osteopenia is provided by several organizations. The prevention and treatment calcium doses continue to be studied but the current recommendations up to this point are presented here. The National Osteoporosis Foundation (NOF), the North American Menopause Society (NAMS), Osteoporosis Canada, and the American Association of Clinical Endocrinologists (AACE) recommend 1,200 mg of calcium daily.[26,30,43,44] Table 4 compares the recommended calcium and vitamin D recommendations from the organizations. The product labeling of all bisphosphonates includes that correction of calcium and vitamin D deficiency is mandatory before initiating therapy.[45-47] None of the guidelines recommend more than 1,500 mg per day of calcium. The length of treatment with calcium is usually considered to be indefinite.

One exception to calcium 1,200 mg daily is if the patient is taking chronic corticosteroids. Corticosteroids decrease calcium intestinal absorption and increase urinary excretion. If a patient is taking chronic corticosteroids (such as prednisone 7.5 mg daily for 3 months), the American College of Rheumatology recommends 1,500 mg of elemental calcium per day.[48]

There are many products and formulations for calcium and patients often present with questions regarding the differences. No formulation is superior to another, but the decision should be based upon the patients' needs, cost, convenience, and availability. The formulations differ in the salt forms and this causes variation in

elemental calcium. Calcium carbonate and citrate are the most common and are usually considered the salt forms of choice. Patients should be instructed to read the supplement facts label to determine the elemental calcium amount and look at the serving size, as it could be representing more than one tablet. Tablet 5 presents examples of combination calcium and vitamin D products. Note that calcium and Vitamin D do not need to be taken together in order to achieve the synergistic benefit.[8]

Calcium carbonate is the most common calcium supplement on the market. It is usually from sources such as rock deposits, limestone, or oyster shell. The lead amount found in oyster shell is not clinically significant since it is such a small amount. Calcium carbonate has the highest elemental calcium content of 40% and should be taken with food since it is better absorbed in an acidic environment. Therefore, it should not be taken in conjunction with histamine-2 blockers or proton pump inhibitors and is not the appropriate form to use in patients taking these medications. Since calcium carbonate supplementation requires gastric acid for optimal absorption, older individuals with reduced gastric acid production should switch to a formulation that doesn't have pH requirements. Carbonate is preferred in patients with renal failure due to its ability to bind with phosphate in the intestines. Calcium carbonate is the most cost effective formulation since a single dose of 500 mg elemental calcium can be packaged into one tablet.[22,23,30,43]

Calcium citrate contains 21% of elemental calcium and does not have a pH requirement for absorption. It is more soluble than calcium carbonate, has better absorption, and may be taken without regard to meals. Some clinicians prefer the citrate form in the older adult because it is better absorbed, less likely to cause constipation, and the older adult is more likely to have GERD and gastric achlorhydria with the use of histamine-2 blockers and proton pump inhibitors. Calcium citrate is an alternative for those who get gastrointestinal effects from taking calcium carbonate. However, calcium citrate is difficult to compact into tablets and therefore multiple tablets must be taken per serving in order to achieve the same amount of elemental calcium as calcium carbonate. Calcium citrate is generally more expensive. [22,23,30,43]

Calcium side effects can include constipation, bloating, and flatulence. Advise the patient to take calcium with food, increase his or her fluid intake and eat more high-fiber foods. If this does not help, it is best for the patient to switch to a different formulation that is better tolerated. Hypercalcemia is not common from administration of oral calcium unless the patient has chronic renal failure. Kidney stones are found to occur when the calcium daily amount exceeds 2,150 mg.[22, 30] The body has a protective mechanism against calcium intoxication by decreasing the efficiency of absorption as consumption increases. Due to this protective mechanism, the body absorbs calcium more efficiently if the patient ingests less than or equal to 500 mg at one time. Therefore, it is recommended that the patient take divided doses throughout the day. If a patient is starting calcium supplements for the first time, advise him or her to titrate up slowly in order to avoid side effects.[26]

Drug interactions are common with calcium as calcium can reduce the absorption of many other medications. Separate calcium from bisphosphonates to prevent reduced absorption. Calcium can also decrease the absorption of iron, levothyroxine, fluoroquinolones, and tetracycline antibiotics.[23]

Vitamin D Supplement Treatment Doses, Guideline Recommendations, and Monitoring

The dose that is most effective for osteoporosis prevention has been stated by IOM, but the dose needed for fall and fracture prevention in patients with osteoporosis or osteopenia has different recommendations from several organizations. The treatment vitamin D dose continues to be studied but the current recommendations up to this point are presented here.

The pharmacist can choose between two types of vitamin D supplements: D_2 (ergocalciferol) or D_3 (cholecalciferol). Calcitriol is not usually recommended for osteoporosis treatment and prevention due to the statistically significant increase in the risk of hypercalcemia.[3] Vitamin D_3 is preferred per many of the organizations but it is not clear if one is superior.[15,26,30,44,49] Vitamin D_3 products are industrially synthesized from irradiation of 7-dihydrocholesterol from lanolin in sheep's wool. Certain individuals might want to avoid using animal products and in those cases, Vitamin D_2 would be

preferred since it is from plant sources. Lanolin is also a common cause of allergic dermatitis and there have been case reports of cholecaciferol allergies because of this cross-reaction.[9] With daily dosing, D_2 and D_3 appear equally potent but with weekly or monthly dosing D_3 appears three times more potent than D_2. Some reports cite that D_2 and D_3 are equivalent but there is not a definite conclusion. It might be that high doses of vitamin D_2 are less potent.[9]

A majority of the guidelines recommend around 800 IU daily of vitamin D. [15,26,30,43, 44,49] Vitamin D products are often combined with calcium products for ease of patient adherence. The usual dose of Vitamin D in a calcium supplement ranges depending on the formulation. In general, combination products will contain between 100 to 600 IU of Vitamin D. Single ingredient vitamin D products include over the counter D_3 products of 400 IU tablets, 1000 IU tablets and capsules, 2000 IU capsules, and 50,000 IU capsules. Vitamin D_2 (Drisdol®) 50,000 IU is a prescription capsule.[29] The duration for vitamin D supplementation is usually considered indefinite.

The dosing amount and frequency for vitamin D deficiency and prevention of falls and fractures has been recommended and studied in a variety of ways. A common dosing schedule seen in practice for vitamin D deficiency is 50,000 IU weekly for six to eight weeks and this regimen can be repeated if the 25(OH)D level does not reach 75 nmol/L (30 ng/ml).[21] Vitamin D 50,000 IU can also be given every two to four weeks to maintain the 25(OH)D level. Ish-Shalom et al. published results from a study in 2008 that compared vitamin D daily, weekly, and monthly dosing.[50] The doses were all diluted in one milliliter of solution and were D_3 1,500 IU daily, 10,500 IU weekly or 45,000 IU every 28 days. This was a small study with 48 female participants with hip fracture for a duration of eight weeks. There was not a statistical difference in the 25(OH)D levels at the end of the eight weeks between the groups. The authors propose that the dosing regimen be chosen based on adherence.

Sanders et al conducted a study to determine whether a single annual dose of vitamin D_3 500,000 IU would improve adherence and reduce the risk of falls and fracture in women.[51,52] Their trial was published in 2010. The study was a single center, double-blind, randomized, placebo controlled trial in Australian women. Participants were included if they were at higher risk of hip fracture such as history of maternal hip fracture, past self-fracture, or self-reported faller. There were a total of 2,256 participants with an average age of 76 years and a median follow up of 2.96 years. The 25(OH)D measurement was only done in a subset of 131 patients. Seventy-four percent of 1,131 women in the vitamin D group and 68% of 1,125 women in the placebo group had at least one fall. One hundred fifty-five women taking vitamin D had 171 fractures and 125 taking placebo had 135 fractures. The vitamin D group fracture rate was 4.9 per 100 person years vs. 3.9 in the placebo group. This vitamin D dose should not be recommended to patients.

The 2010 International Osteoporosis Foundation (IOF) position statement reports that the serum 25(OH)D concentration is the best available clinical indicator of vitamin D status.[15] Other organizations generally agree that it is a good biomarker of exposure but it has not been correlated well to outcomes.[9] The IOF statement includes that the 25(OH)D concentration declines with age but that the concentration response to a dose of vitamin D_3 is not affected by age. It also acknowledges that the serum 25(OH)D levels vary across commonly used assays. The NOF recommends measurement of 25(OH)D in patients at risk of vitamin D deficiency such as patients with low bone mass.[26] The NOF recommends that serum 25(OH)D levels be checked in patients with malabsorption syndromes (such as celiac disease), chronic renal insufficiency, and homebound patients. Osteoporosis Canada recommends that all patients taking medications for osteoporosis should have a 25(OHD)D level checked along with patients who have had a fracture or a comorbid condition (including corticosteroid use) for vitamin D deficiency.[44,49] It is not meant to be checked in healthy individuals.

Vitamin D deficiency is generally considered to be less than 50 nmol/L (20 ng/ml). The majority of the IOF Working Group members recommend a target level of 75 nmol/L (30 ng/ml) for older adults and several members voted for 50 to 75 nmol/L (20 to 30 ng/ml) as the target level for fall and fracture prevention.[15] To convert between 25(OH)D nmol/L and ng/ml, multiply nmol/L by 0.4 to get the ng/ml.[53] AACE recommends levels between 75 and 150 nmol/L (30 and 60 ng/mL). A 25(OH)D is not recommended to be higher than 150 nmol/L (60 ng/ml).[43] IOM reported that 50 nmol/L (20

ng/ml) is sufficient for bone health and levels over 75 nmol/L (30 ng/ml) have not consistently been shown to have health benefits.[22]

The estimated average vitamin D requirement for older adults to reach a serum 25(OH)D level of 75 nmol/L (30 ng/ml) is 800 to 1,000 IU per day. The IOF does not recommend higher intakes than the general recommendation of 1,000 IU per day for older adults due to a lack of the higher dose evaluation in clinical trials.[15] For patients who are obese, have osteoporosis, or receive limited sun exposure, 2,000 IU per day is recommended. A general calculation is each 100 IU of added vitamin D will increase the serum 25(OH)D level by about 2.5 nmol/L (1 ng/ml).[30,43] Other studies have shown 25(OH)D levels increase in response to increased vitamin D intake but the relationship might not be linear. The amount of the increase depends on the starting serum level and duration of supplementation.[53] Another source said 1,700 IU/day was needed to raise 25(OH)D from 50 to 80 nmol/L (20 to 32 ng/ml).[9]

The treated individual should be retested after three to four months to determine if the 25(OH)D level has increased to the desired target.[30,44] The half-life of 25(OH)D is 15 days, so there is no need to retest the level sooner.

Vitamin D toxicity symptoms include vague symptoms of anorexia, polyuria, and heart arrhythmias. Hypercalcemia leading to kidney stones is a consequence of vitamin D toxicity. Doses greater than 10,000 IU/day increase the risk of hypercalciuria and hypercalcemia. Drug interactions include prednisone which impairs vitamin D metabolism. Orlistat and cholestyramine prevent absorption of vitamin D. Phenobarbital and phenytoin increase the metabolism of D to inactive forms and reduce calcium absorption.[9,29]

Conclusion

The conclusions are not straight forward. The optimal supplement amount of calcium and vitamin D conflict between studies and guidelines and a moderate decision is appropriate at this time. In a patient with osteoporosis, calcium 1,200 mg and vitamin D 800 IU daily is appropriate. The link between calcium and cardiovascular risk is preliminary, but the take away point is to encourage dietary calcium be the main source of the 1,200 mg and only recommend a supplement when it is lacking in the diet.

It is imperative to continually re-examine the most current knowledge regarding calcium and vitamin D in order to make sound professional judgments for the safety of patients. New information continues to be reported; refer to Table 6 for references to keep up to date on calcium, vitamin D, and osteoporosis. Pharmacists must keep in mind that first, do no harm, and treat the patient if the benefit outweighs the risk.

Table 1: IOM Dietary Reference Intakes (DRI) for Calcium and Vitamin D[22]

	Calcium (mg/day)			Vitamin D (IU/day)		
Life Stage Group	*EAR*	*RDA*	*UL*	*EAR*	*RDA*	*UL*
31-50 years of age	800	1,000	2,500	400	600	4,000
51-70 years of age for males	800	1,000	2,000	400	600	4,000
51-70 years of age for females	1,000	1,200	2,000	400	600	4,000
>70 years of age	1,000	1,200	2,000	400	800	4,000

EAR: Estimated Average Requirement
RDA: Recommended Dietary Allowance
UL: Upper Level Intake

Table 2: Selected Food Sources of Calcium[54-56]

Food	Serving Size	Calcium per serving (mg)
Dairy Products		
Cheese (cheddar, swiss)	1.5 ounces	275-336
Cheese, cream, regular	1 tablespoon	12
Cottage cheese, 1% milk fat	8 ounces	138
Frozen yogurt, vanilla, soft serve	4 ounces	103
Ice cream, vanilla	4 ounces	150
Milk (whole, reduced-fat, non-fat)	8 ounces	285-302
Milkshake	8 ounces	300
Pudding, instant, (chocolate, banana, etc.) made with 2% milk	4 ounces	153
Sour cream	2 tablespoons	32
Yogurt, plain, low-fat, or fruit	8 ounces	245-452
Fish		
Salmon, canned, with edible bones	3 ounces	181
Sardines, canned in oil, with edible bones	3 ounces	324
Nuts		
Almonds	12	70
Walnuts	12 halves	38
Vegetables		
Broccoli, raw	8 ounces	90
Soybeans, cooked	8 ounces	261
Spinach, cooked	4 ounces	120
Turnip greens, boiled	4 ounces	99
Fortified Foods		

Bread	1 slice	20-31
Cereal	8 ounces	100-1000
Oatmeal, instant	1 packet	99-110
Orange juice	6 ounces	200-260
Soy beverage	8 ounces	80-500

Table 3: Selected Food Sources of Vitamin D[9, 27, 54, 55]

Food	**Serving Size**	**International Units (IUs) per serving**
Cereal, vitamin D fortified	8 ounces	40-100
Egg yolk	1	20
Milk, vitamin D fortified	8 ounces	115-124
Orange juice, vitamin D fortified	8 ounces	100
Salmon (sockeye)	3 ounces	447
Tuna fish, canned in water	3 ounces	154
Yogurt, vitamin D fortified	6 ounces	80

Table 4: Comparison of recommended daily calcium and vitamin D for prevention and treatment of osteoporosis [15,26,30,43,44,48]

Organization	Target Population	Recommended Elemental Calcium Amount (mg/day)	Recommended Vitamin D Amount (IU/day)	Preferred Type of Vitamin D
National Osteoporosis Foundation (NOF)	Postmenopausal women and men age 50 and older	1,200 (UL of 1,500)	800 to 1,000	D_3
North American Menopause Society (NAMS)	Women age 50 and over	1,200	800 to 1,000 (UL of 2,000)	D_3
American Association of Clinical Endocrinologists (AACE)	Postmenopausal women	1,000 to 1,200	400 to 800	No preference stated
American College of Rheumatology (ACR)	Patients taking oral glucocorticoids for any dose or duration	1,200 to 1,500	800 to 1,000	No preference stated
International Osteoporosis Foundation (IOF)	Older adults	Not addressed	800 to 1,000 (UL of 2,000)	D_3
Osteoporosis Canada	Adults age 50 and over	1,200	800 to1,000 (UL of 2,000)	D_3

Table 5: Common Calcium and Vitamin D OTC Combination Products[57-62]

	Brand Name	Amount of Elemental Calcium (per tablet/soft chew/chewable)	Amount of Vitamin D (per tablet/soft chew/chewable)	Other Active Ingredients
Calcium Carbonate	Caltrate® 600 + D (tablets & soft chews)	600 mg	400 IU (D_3)	--
	Caltrate® 600 + D Plus Minerals (tablets)	600 mg	400 IU (D_3)	Magnesium 50 mg Manganese 1.8 mg Boron 250 mcg Zinc 7.5 mg Copper 1 mg
	Caltrate® 600 + D Plus Minerals Chewables	600 mg	400 IU (D_3)	Magnesium 40 mg Manganese 1.8 mg Boron 250 mcg Zinc 7.5 mg Copper 1 mg
	Nature Made® Calcium 500 mg with Vitamin D	500 mg	200 IU	--
	Nature Made® Calcium 600 mg with Vitamin D	600 mg	200 IU	--
	Nature Made® Calcium 750 mg + D + K	750 mg	500 IU	Vitamin K 40 mcg
	Nature Made® Calcium Magnesium & Zinc	333 mg	200 IU	Magnesium oxide 133 mg Zinc 5 mg
	Oscal® Calcium + D_3	500 mg	200 IU	--
	Oscal® Chewable	500 mg	600 IU	--
	Oscal® Extra D_3	500 mg	600 IU	--
	TUMS® Regular	200 mg	--	--
	TUMS® Extra	300 mg	--	--
	TUMS® Smoothies	300 mg	--	--
	TUMS® Ultra	400 mg	--	--
	Viactiv®	500 mg	500 IU (D_3)	Vitamin K 40 mcg
Calcium Citrate	Citrical® Regular	250 mg	200 IU (D_3)	--
	Citrical® Petites with Vitamin D	200 mg	250 IU(D_3)	--
	Citrical® Maximum Caplets	315 mg	250 IU(D_3)	--

	Citrical® Plus with Magnesium	250 mg	125 IU(D_3)	Magnesium 40 mg Manganese 0.5 mg Boron 250 mcg Zinc 3.75 mg Copper 0.5 mg

Table 6: Calcium and Vitamin D Additional Resources

Name	Web address	Information Available
Institute of Medicine	www.iom.edu/calcium	Dietary reference intakes for calcium and vitamin D
National Institutes of Health: Office of Dietary Supplements	www.ods.od.nih.gov	Supplement information with recommended intakes, dietary sources, health outcomes, adverse reactions, and toxicities
The National Osteoporosis Foundation	www.nof.org	Osteoporosis information for patients and health care professionals
International Osteoporosis Foundation	http://www.iofbonehealth.org/	Osteoporosis information for patients and health care professionals
U.S. Department of Health and Human Services: Agency for Healthcare Research and Quality	www.ahrq.gov	Comparative efficacy information for disease states and medications for patients and health care professionals
FRAX WHO Fracture Risk Assessment Tool	http://www.sheffield.ac.uk/FRAX/tool.jsp	World Health Organization Tool to assess individual patient risk of 10-year probability of fracture using bone mineral density and patient clinical risk factors