

NATURAL MEDICINES COMPREHENSIVE DATABASE



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VITAMIN D

Also Known As:

Alfacalcidol: 1-alpha-hydroxycholecalciferol, 1-alpha-hydroxycholécalfiférol, 1 alpha (OH)D3.

Calcifediol: 25-HCC, 25-hydroxycholecalciferol, 25-hydroxycholécalfiférol, 25-hydroxyvitamin D3, 25-hydroxyvitamine D3, 25-OHCC, 25-OHD3, Calcifédiol.

Calcipotriene: Calcipotriène, Calcipotriol.

Calcitriol: 1,25-DHCC, 1,25-dihydroxycholecalciferol, 1,25-dihydroxycholécalfiférol, 1,25-dihydroxyvitamin D3, 1,25-dihydroxyvitamine D3, 1,25-diOHC, 1,25(OH)2D3.

Cholecalciferol: 7-déhydrocholestérol Activé, Activated 7-dehydrocholesterol, Cholécalfiférol, Colecalciferol, Colécalfiférol, Vitamin D3.

Dihydrotachysterol: DHT, Dihydrotachystérol, dihydrotachysterol 2, dichysterol, Vitamine D3.

Ergocalciferol: Activated Ergosterol, Calciferol, Ergocalciférol, Ergocalciferolum, Ergostérol Activé, Irradiated Ergosterol, Ergostérol Irradié, Viosterol, Viostérol, Vitamin D2, Vitamine D2.

Paricalcitol: 19-nor-1,25-dihydroxyvitamin D2, 19-nor-1,25-dihydroxyvitamine D2, Paracalcin.

Fat-Soluble Vitamin, Vitamina D, Vitamine D, Vitamine Liposoluble, Vitamine Soluble dans les Graisses.

Scientific Name:

1,25-dihydroxycholecalciferol; 25-hydroxycholecalciferol; Alfacalcidol; Calcifediol; Calcipotriene; Calcitriol; Cholecalciferol; Dihydrotachysterol; Ergocalciferol; Paricalcitol.

People Use This For:

Orally, vitamin D is used for preventing osteoporosis, muscle weakness, enhancing immune function, preventing autoimmune diseases, multiple sclerosis, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), asthma, bronchitis, and cancer. It is also used orally for rickets, premenstrual syndrome (PMS), influenza, preventing falls and fractures in people at risk for osteoporosis, corticosteroid-induced osteoporosis, osteomalacia, anticonvulsant-induced osteomalacia, renal osteodystrophy, osteitis fibrosa in people on dialysis, hepatic osteodystrophy, and osteogenesis imperfecta. Vitamin D is also used for preventing and treating hypocalcemia and tetany in premature infants' bone disorders in people with familial hypophosphatemia, hypophosphatemia associated with Fanconi syndrome, and hypocalcemia associated with postoperative or idiopathic hypoparathyroidism or pseudohypoparathyroidism. Other uses include plaque-type psoriasis, actinic keratosis, lupus vulgaris, squamous cell carcinomas, vitiligo, scleroderma, myelodysplastic

syndrome, periodontal disease, hypertension, hyperlipidemia, cardiovascular disease, obesity, and diabetes. Vitamin D is also used orally to treat severe proximal myopathy associated with vitamin D deficiency or myopathy associated with the use of HMG-CoA reductase inhibitors (statin-induced myopathy), and to maintain bone density in prostatic cancer patients at risk for osteoporosis when treated with luteinizing hormone-releasing hormone analogue (LHRH-a).

Topically, vitamin D is used as calcitriol or calcipotriene for plaque-type psoriasis. Intravenously, vitamin D, administered as calcitriol, is used for hypocalcemic tetany in premature infants, hypocalcemia and hyperparathyroidism in renal dialysis patients, and osteitis fibrosa.

Intramuscularly, vitamin D is administered as ergocalciferol for hepatic osteodystrophy, as an injectable source of vitamin D, and to treat severe proximal myopathy associated with vitamin D deficiency.

Safety:

LIKELY SAFE ...when used orally or intramuscularly and appropriately. Vitamin D has been safely used in a wide range of doses (7555, 16888, 16891, 17476). When used orally long-term, doses should not exceed the tolerable upper intake level (UL) of 4000 IU per day for adults (17506); however, much higher doses such as 50,000 IU/week orally for 6-12 weeks are often needed for the short-term treatment of vitamin D deficiency (16891, 17476). Optimal blood levels of 25-hydroxyvitamin D for maintaining bone density is 30-100 ng/mL. Toxicity usually does not occur until levels exceed 150 ng/mL (17476).

POSSIBLY UNSAFE ...when used orally in excessive doses, long-term. Taking doses greater than the tolerable upper intake level (UL) of 4000 IU per day for long periods can increase the risk of hypercalcemia (17506); however, much higher doses are often needed for short-term treatment of vitamin D deficiency. Optimal blood levels of 25-hydroxyvitamin D for maintaining bone density is 30-100 ng/mL. Toxicity usually does not occur until levels exceed 150 ng/mL (17476).

CHILDREN: LIKELY SAFE ...when used orally and appropriately. When used long-term, doses should not exceed the tolerable upper intake level (UL). Infants from 0-6 months should not exceed the UL of 1000 IU daily. Infants aged 6-12 months should not exceed the UL of 1500 IU daily. Children aged 1-3 years should not exceed the UL of 2500 IU daily. Children aged 4-8 years should not exceed the UL of 3000 IU daily. Children aged 9 years and older should not exceed the UL of 4000 IU daily (17506); however, much higher doses are often needed for the short-term treatment of vitamin D deficiency. Some research shows that giving vitamin D 14,000 IU/week for a year in children aged 10-17 is safe (16875). **POSSIBLY UNSAFE** ...when used orally in excessive doses, long-term. Taking doses greater than the tolerable upper intake level (UL) long-term can increase the risk of hypercalcemia. Infants from 0-6 months should not exceed the UL of 1000 IU daily. Infants aged 6-12 months should not exceed the UL of 1500 IU daily. Children aged 1-3 years should not exceed the UL of 2500 IU daily. Children aged 4-8 years should not exceed the UL of 3000 IU daily. Children aged 9 years and older should not exceed the UL of 4000 IU daily (17506); however, much higher doses are often needed for the short-term treatment of vitamin D deficiency. Some research shows that giving vitamin D 14,000 IU/week for a year in children aged 10-17 is safe (16875).

PREGNANCY: LIKELY SAFE ...when used orally and appropriately. Vitamin D is safe when used in doses below the tolerable upper intake level (UL) of 4000 IU per day (17506). **POSSIBLY UNSAFE** ...when used orally in excessive amounts. Tell

patients not to use doses above the tolerable upper intake level (UL) of 4000 IU per day. Hypercalcemia during pregnancy due to excessive vitamin D intake can lead to several adverse effects in the fetus including suppression of parathyroid hormone, hypocalcemia, tetany, seizures, aortic valve stenosis, retinopathy, and mental and/or physical retardation in the infant (17506).

LACTATION: LIKELY SAFE ...when used orally and appropriately. Vitamin D is safe when used in doses below the tolerable upper intake level (UL) of 4000 IU per day (17506). **POSSIBLY UNSAFE** ...when used orally in excessive amounts. Tell patients not to use doses above the tolerable upper intake level (UL) of 4000 IU per day (17506).

Effectiveness:

EFFECTIVE

Familial hypophosphatemia. Taking calcitriol or dihydrotachysterol orally in conjunction with phosphate supplements is effective for treating bone disorders in people with familial hypophosphatemia (11818).

Fanconi syndrome. Taking ergocalciferol orally is effective for treating hypophosphatemia associated with Fanconi syndrome (11819).

Hypoparathyroidism. Taking dihydrotachysterol or calcitriol orally is effective for increasing serum calcium concentrations in people with hypoparathyroidism or pseudohypoparathyroidism. Ergocalciferol is effective in high doses for increasing serum calcium concentrations in people with hypoparathyroidism or pseudohypoparathyroidism (11820).

Osteomalacia. Taking cholecalciferol is effective for treating osteomalacia. Calcifediol orally is effective for treating osteomalacia secondary to liver disease (hepatic osteodystrophy), and anticonvulsant-induced osteomalacia. Ergocalciferol is effective for osteomalacia due to malabsorption syndromes and corticosteroid-induced osteomalacia (11821).

Psoriasis. Applying calcipotriene topically effectively treats plaque-type psoriasis in some patients (11822).

Renal osteodystrophy. Taking calcifediol orally manages hypocalcemia and prevents renal osteodystrophy in people with chronic renal failure undergoing dialysis (11823).

Rickets. Vitamin D is effective for preventing and treating rickets. Calcitriol should be used in patients with renal failure (11824).

Vitamin D deficiency. Vitamin D is effective for preventing and treating vitamin D deficiency using a wide range of doses (7555, 16888, 16891, 17476). Optimal blood levels of 25-hydroxyvitamin D for maintaining bone density is 30-100 ng/mL. Toxicity usually does not occur until levels exceed 150 ng/mL (17476).

LIKELY EFFECTIVE

Corticosteroid-induced osteoporosis. Taking calcifediol or cholecalciferol orally prevents corticosteroid-induced osteopenia and osteoporosis (7555).

Fall prevention. Vitamin D deficiency is linked to an increased risk of falls in older adult patients. Clinical research also shows that taking a vitamin D supplement 700-1000 IU/day reduces the risk of falling (11916, 11917, 11918, 11939, 14291, 15606, 16275). An analysis of studies suggests that taking vitamin D supplements can reduce falls by 22% in older adults. To prevent one fall, 15 older adults would need to take a vitamin D supplement. This risk reduction appears to be independent of calcium supplementation, but some experts think a combination of calcium and vitamin D may be important (11916).

Some evidence shows that higher doses of vitamin D are more effective than lower

doses. In one study, vitamin D (ergocalciferol) 800 IU daily significantly reduced the risk of falling compared to placebo; however, lower doses were not effective (15606). Vitamin D, in combination with calcium, but not calcium alone, may prevent falls by decreasing body sway and systolic blood pressure instead of increasing bone mass strength (6362, 11939). Some evidence also shows that higher serum levels of vitamin D is associated with improved lower-extremity function in people aged 60 years or older (15636).

There might be different effects in women compared to men. In one study, women aged 65 years or older had a 46% lower risk of falling if they took vitamin D 700 IU/day plus calcium citrate 500 mg/day over a 3-year period; however, the combination of vitamin D plus calcium did not decrease falls in men (14291).

Osteoporosis. Most clinical research shows that taking vitamin D (cholecalciferol) orally with calcium supplements can decrease postmenopausal bone loss, help prevent osteoporosis, and decrease the risk of fractures (980, 1836, 6362, 8818, 10932, 12926, 12930, 12933, 12934, 12952). According to one analysis, taking oral vitamin D (cholecalciferol) 700-800 IU daily with or without calcium significantly reduces fracture risk in ambulatory and institutionalized elderly people. The number needed to treat for vitamin D 800 IU taken daily for 2-5 years is 27 patients to prevent one nonvertebral fracture and 45 patients to prevent one hip fracture (12933); however, a subsequent analysis shows that adequate calcium intake is needed along with vitamin D to significantly reduce fracture risk (15633).

Some research has not found a positive effect of vitamin D on fracture risk. A large-scale study in postmenopausal women aged 50-79 years found that taking calcium 1000 mg plus vitamin D (cholecalciferol) 400 IU daily for 7 years only modestly improved bone mineral density and did not significantly reduce fracture risk. But adherence to the treatment regimen was low. In women who were at least 80% adherent, the combination did significantly reduce the risk of hip fractures by about 29% (14282).

Some evidence suggests that cholecalciferol (vitamin D3) in doses of 400 IU/day or less is not effective for fracture prevention (10140, 12933). Another clinical trial found that taking vitamin D (cholecalciferol) 800 IU/day plus calcium 1200-1500 mg/day for 2 years did not significantly increase bone mineral density in African-American postmenopausal women (16878).

There is concern that vitamin D might not be effective for secondary prevention of fractures in elderly patients. Vitamin D (cholecalciferol) 800 IU/day with or without calcium 1000 mg/day for 2-5 years does not significantly reduce fracture risk in elderly women or men who have had a previous fracture compared to placebo (13073). Another study also suggests that vitamin D (cholecalciferol) 800 IU/day plus calcium 1000 mg/day might not prevent a second fracture in elderly patients, or prevent a first fracture in elderly patients with other risk factors such as low body weight (under 58 kg, 127.6 pounds), smoking, family history of hip fracture, or fair or poor self-reported health (12929). However, these studies have been criticized for failing to measure vitamin D levels and low adherence to study protocol (12931). One of these studies did not use a placebo control (12929).

Giving vitamin D orally to breast-fed infants seems to help increase bone mineral density. In a retrospective study, prepubertal girls who received vitamin D in infancy had significantly greater bone mineral density at some skeletal sites compared to girls that did not receive vitamin D during infancy (3464).

Taking alfalcidol orally seems to maintain bone density in prostatic carcinoma patients at risk for osteoporosis when treated with luteinizing hormone-releasing hormone analogue (LHRH-a). Alfalcidol maintains but does not increase bone

mineral density (6360).

POSSIBLY EFFECTIVE

Cancer. Clinical research shows that healthy postmenopausal women who take supplemental calcium 1400-1500 mg/day plus vitamin D3 (cholecalciferol) 1100 IU/day have a 60% lower relative risk for developing cancer of any type (15629). This corresponds to a number needed to treat (NNT) of 25. To prevent one occurrence of cancer, 25 postmenopausal women would need to receive this combination of calcium plus vitamin D for 4 years. Taking calcium alone did not significantly reduce the risk of cancer, which suggests that the vitamin D component is important. Other evidence related specifically to colorectal cancer also shows that people with below average vitamin D levels don't seem to get any benefit from taking calcium supplements for cancer prevention (12118).

Some epidemiological evidence shows that higher vitamin D serum levels as a result of increased vitamin D intake from food and supplements, increased sun exposure, and other factors is associated with a reduced risk of cancer and cancer-related mortality in men. Men with the highest level of vitamin D, corresponding to a 25 nmol/L higher serum concentration, have a 17% reduction in overall cancer incidence, 29% reduction in cancer-related mortality, 43% reduction in gastrointestinal cancer incidence, and 45% reduction in gastrointestinal cancer-related mortality (14320). Other epidemiological research is conflicting. In another study, higher vitamin D serum levels in men and women were associated with a decreased risk of colorectal cancer-related mortality. However, higher vitamin D serum levels were not associated with a reduced risk of mortality related to other types of cancer (16103).

Hyperparathyroidism-related bone loss. Taking cholecalciferol orally seems to help decrease secondary hyperparathyroidism and bone turnover in women. In one study, supplementation with cholecalciferol resulted in increased serum levels of 25-hydroxyvitamin D, reduced levels of parathyroid hormone, and decreased production of markers of bone turnover (3463).

Multiple sclerosis (MS). Population research suggests that long-term vitamin D supplementation decreases the risk of MS in women by up to 40%. The effect seems to be dose-dependent. Consumption of at least 400 IU per day, mainly in the form of a multivitamin supplement, appears to have the greatest protective effect (11356).

Additional population research in over 7 million people shows that higher levels of 25-hydroxyvitamin D levels, a reliable measure of vitamin D status, are associated with a significantly lower risk of developing MS. In white men and women, for every 50 nmol/L increase in 25-hydroxyvitamin D levels, there appears to be a 41% decrease in MS risk. However, in black and Hispanic men and women, 25-hydroxyvitamin D levels were not associated with MS risk (15159).

Respiratory tract infections. Some clinical research shows that taking vitamin D (cholecalciferol) 1200 IU daily during the winter significantly reduces the risk of developing seasonal flu by about 42% in school aged children compared to placebo (17486). Preliminary clinical research also shows that taking vitamin D 500 IU/day between the months of September and July significantly reduces the risk of asthma exacerbation triggered by an acute respiratory tract infection in children (17687).

Population research suggests that low vitamin D levels are associated with increased risk of upper respiratory tract infection in children (17686).

Rheumatoid arthritis (RA). Population research suggests that older women who have a higher intake of vitamin D from foods or supplements tend to have a lower risk of developing RA (12206).

Tooth retention. Taking calcium and vitamin D orally appear to beneficially affect

tooth retention in the elderly population (8816).

Weight loss. Population research shows that people with lower vitamin D levels are significantly more likely to be obese compared to people with higher vitamin D levels (15630). Evidence from a large-scale, high-quality trial also shows that postmenopausal women taking calcium 1000 mg plus vitamin D (cholecalciferol) 400 IU daily for 3 years are significantly less likely to gain small to moderate amounts of weight compared to women taking placebo. Women taking calcium plus vitamin D are also more likely to lose weight and maintain their weight. This beneficial effect is mainly seen in women who have inadequate intake of calcium, less than 1200 mg/day, prior to starting a calcium supplement (15604).

POSSIBLY INEFFECTIVE

Breast cancer. There is conflicting evidence about the effects of vitamin D on breast cancer risk. Some population research evaluating intake levels of calcium plus vitamin D suggests that higher intake of calcium is associated with a significantly reduced risk of developing breast cancer in premenopausal women; however, vitamin D intake alone was not associated with a significantly reduced risk of breast cancer. Neither calcium nor vitamin D were associated with a reduced risk of breast cancer in postmenopausal women (15631). Contradictory research suggests that higher vitamin D serum levels are associated with a reduced risk of breast cancer. In an analysis of studies evaluating the association between vitamin D serum levels and breast cancer risk, women with serum levels of about 52 ng/mL had a 50% lower risk of developing breast cancer compared to women with serum levels of less than 13 ng/mL. However, this high serum level of vitamin D corresponds to a high dose of vitamin D of about 4000 IU/day (16049).

The best evidence to date, from a large scale clinical trial (Women's Health Initiative), shows that postmenopausal women who take vitamin D (cholecalciferol) 400 IU/day plus calcium 1000 mg/day for 7 years do not have a significantly reduced risk of developing breast cancer (16715). However, it is unknown if higher vitamin D doses might have an effect on breast cancer risk.

Hypertension. Population research suggests that lower vitamin D levels are associated with a higher risk of developing hypertension compared to people with higher vitamin D levels (15630); however, a large scale clinical trial shows that taking vitamin D (cholecalciferol) 400 IU/day in combination with 1000 mg/day of elemental calcium does not significantly lower blood pressure or reduce the risk of developing hypertension in postmenopausal women (16714).

Muscle strength. Oral cholecalciferol 1000 IU per day doesn't seem to increase muscle strength or improve physical performance in healthy older men who are not vitamin D deficient (11814).

Renal transplant-related bone loss. Calcitriol 0.25 mcg per day in combination with calcium carbonate 500 mg per day doesn't significantly decrease bone loss associated with long-term renal transplantation; however, calcitriol might reduce osteoclast suppression, help maintain trabecular bone volume and wall thickness, and improve axial bone mineral density (4823).

INSUFFICIENT RELIABLE EVIDENCE to RATE

Asthma. Population research suggests that low vitamin D levels might increase the risk of asthma and increase the risk of asthma exacerbations in children (17685, 17686). Preliminary clinical research shows that taking vitamin D 500 IU/day between the months of September and July significantly reduces the risk of asthma exacerbation triggered by an acute respiratory tract infection in children (17687). Some research also suggests that vitamin D deficiency might result in increased usage of inhaled and oral

corticosteroids (17686).

Some research suggests that vitamin D intake during pregnancy might also reduce the risk of asthma and wheezing in children. However, contradictory evidence suggests that increased vitamin D levels during pregnancy might actually increase risk of asthma (17685). Additionally, other population research suggests that administering vitamin D during the first year of life could increase the risk of asthma, atopy, eczema, and allergic rhinitis later in life (17686).

Cardiovascular disease. Population research suggests that people with vitamin D levels below 15 ng/mL have a significantly increased risk of developing cardiovascular disease including myocardial infarction, stroke, heart failure, cardiovascular mortality and all-cause mortality compared to those with higher vitamin D levels (16615, 16617, 16618). Another population study suggests people on dialysis who have vitamin D levels less than 17.8 ng/mL have a higher risk of all-cause mortality compared to people with higher levels; however, low vitamin D levels were not significantly associated with cardiovascular mortality (16619).

Additional population research suggests that people with lower vitamin D levels are more likely to have cardiovascular disease risk factors, including type 2 diabetes, obesity, hypertension, and hyperlipidemia, compared to people with higher vitamin D levels (15630).

However, in a large-scale clinical trial, taking vitamin D (cholecalciferol) 200 IU plus calcium 500 mg twice daily did not significantly reduce the risk of cardiovascular events such as myocardial infarction or stroke (16616).

Chronic obstructive pulmonary disease (COPD). Low vitamin D levels are associated with reduced lung function. In population research, many patients with COPD have also been found to have reduced vitamin D levels (17685). However, there is no reliable clinical research showing that taking a vitamin D supplement can reduce symptoms of COPD.

Colorectal cancer. The role of vitamin D in colorectal cancer is not clear. Some research shows that high intake of dietary or supplemental calcium is associated with a reduced risk of adenoma recurrence and colorectal cancer (970, 994, 1047, 8820, 12118, 12120, 12950). Vitamin D seems to be an important factor. People with lower than average vitamin D levels do not seem to get any benefit from calcium supplements (12118). However, contradictory research suggests that postmenopausal women who take calcium 1000 mg/day plus vitamin D 400 IU/day do not have a reduced risk of developing colorectal cancer (14290). This finding may not be reliable due to the high baseline intake of calcium in study participants.

Epidemiological research in men suggests that higher vitamin D serum levels correspond with a reduced incidence of gastrointestinal cancers and cancer-related mortality. Men with the highest level of vitamin D, corresponding to a 25 nmol/L higher serum concentration, have a 43% reduction in gastrointestinal cancer incidence, and 45% reduction in gastrointestinal cancer-related mortality (14320). In another study, higher vitamin D serum levels in men and women were associated with a decreased risk of colorectal cancer-related mortality (16103).

Additionally, in an analysis of studies evaluating the association between vitamin D serum levels and colorectal cancer risk, people with serum vitamin D levels of 33 ng/mL or greater have a 50% lower risk of developing colorectal cancer compared to people with levels of 12 ng/mL or less (16101).

Diabetes. Population research shows that people with lower vitamin D levels have a significantly higher risk of type 2 diabetes compared to people with higher vitamin D levels (15630, 16713); however, it is unclear if vitamin D is associated with reduced risk independent of calcium intake (16713).

There is no reliable evidence that taking vitamin D supplements can treat or prevent type 2 diabetes (16713). However, there is preliminary evidence that daily vitamin D supplementation in infants during the first year of life is associated with a reduced incidence of type 1 diabetes development later in life (10139).

Heart failure. Population research suggests that people with vitamin D levels below 15 ng/mL have a significantly increased risk of developing cardiovascular disease, including heart failure, compared to those with higher vitamin D levels (16615).

However, in a clinical trial, taking vitamin D (cholecalciferol) 2000 IU daily did not decrease the risk of mortality compared to placebo in New York Heart Association (NYHA) class 2 heart failure patients (16620).

Hyperlipidemia. Population research shows that people with lower vitamin D levels are significantly more likely to have hypercholesterolemia and hypertriglyceridemia compared to people with higher vitamin D levels (15630). Preliminary clinical research shows that taking calcium 1200 mg daily plus vitamin D 400 IU daily, in combination with calorie restriction, significantly reduces the total cholesterol:HDL ratio and the LDL:HDL ratio in overweight or obese women; however, calcium plus vitamin D did not significantly reduce total or LDL cholesterol compared to placebo (15601).

Metabolic syndrome. There is conflicting evidence about the association between vitamin D and metabolic syndrome. Some population research suggests that women aged 45 years and older with a higher intake of vitamin D from diet and supplements do not have a lower risk of developing metabolic syndrome independent of calcium intake compared to women with lower vitamin D intake (14265). However, other population research suggests that higher vitamin D levels are associated with a lower risk of metabolic syndrome (16713).

Overall mortality. Population studies suggest that low serum levels of vitamin D are associated with an increased risk of mortality from any cause. An analysis of vitamin D clinical trials suggests that people who take vitamin D supplements in a dose of 300-2000 IU/day, or an average of 528 IU/day, have a 7% lower relative risk of dying from any cause compared to control (16102). A separate analysis of population-based studies evaluating vitamin D in women aged 70-79 additionally found mortality from any cause was reduced by half in women with serum 25-hydroxy vitamin D levels higher than 64.7 nmol/L, compared to those with serum levels less than 38.2 nmol/L (16872).

Myelodysplastic syndrome. Taking calcitriol or calcifediol orally seems to help myelodysplastic syndrome (11825).

Periodontal disease. Population research shows that higher blood levels of vitamin D are associated with a reduced risk of periodontal disease in adults 50 years of age or older; however, this association was not found for adults younger than 50 years (15634).

Premenstrual syndrome (PMS). There is preliminary evidence that increasing intake of vitamin D from diet or supplements decreases the risk of developing PMS or decreases PMS symptom severity (13094, 16869). Women with an average vitamin D intake of 706 IU/day seem to have about a 40% lower risk of developing PMS compared to women with an average vitamin D intake of 112 IU/day (13094); however, taking vitamin D supplements does not appear to be associated with the risk of developing PMS. However, a clinical study shows that taking vitamin D in combination with calcium 500 mg might significantly decrease the severity of PMS symptoms (16869).

Proximal myopathy. Administering ergocalciferol intramuscularly or taking ergocalciferol orally seems to help treat severe proximal myopathy associated with severe vitamin D deficiency. Several case reports suggest vitamin D therapy can provide prompt relief of muscle weakness and restore mobility (11923).

Statin-induced myalgia. Anecdotal reports suggest that taking oral vitamin D supplements can decrease symptoms of myalgia in patients taking statin drugs. In several reports, patients who discontinued statins due to myalgia were able to resume statin therapy after starting vitamin D supplements. The majority of patients with myalgia were found to be vitamin D deficient with 25-OH vitamin D levels less than 30 nmol/L before starting a supplement (16829). An observational study also found that administering 50,000 units of ergocalciferol once a week for 12 weeks reversed symptoms of myalgia in 92% of statin treated patients with low serum 25-OH vitamin D levels of less than 32 ng/mL (16831).

Vaginal atrophy. Preliminary clinical research shows that taking a vitamin D supplement for at least one year improves the maturation index of superficial vaginal wall cells compared to women who don't take vitamin D. However, symptoms of vaginal atrophy were not different between groups (16879).

Warts. Anecdotal reports suggest that a topical vitamin D3 derivative, maxacalcitol, can reduce viral warts in immunocompromised patients with recalcitrant warts (15635). More evidence is needed to rate vitamin D for these uses.

Mechanism of Action:

Vitamin D is a fat-soluble vitamin. The term vitamin D refers to several forms of vitamin D. There are 2 forms that are physiologically important, ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Ergocalciferol comes from ergosterol, a plant sterol, and yeast. Cholecalciferol is synthesized in the skin via 7-dehydrocholesterol, a cholesterol precursor.

Both ergocalciferol and cholecalciferol are biologically inert and require hydroxylation in the body to form the active metabolite, calcitriol (7555, 16890). Since the early 1900s, ergocalciferol and cholecalciferol have been considered to be equally potent and effective in humans; however, more recently research shows that cholecalciferol is significantly more potent than ergocalciferol. Ergocalciferol appears to be less than one-third the potency of cholecalciferol. Both forms of vitamin D are well absorbed, but cholecalciferol appears to be more efficient in raising 25-hydroxyvitamin D serum levels, which is the best measure of vitamin D status (11937, 11938, 15263, 15264, 16119). Blood concentrations of 50 nmol/L (20 ng/mL) are considered the minimal level to meet bodily needs and lower amounts are considered a deficiency. Higher concentrations of 80 nmol/L (30 ng/mL) are generally preferred (15638). Most laboratories consider the "normal" range to be 50 nmol/L to 250 nmol/mL (16119).

Very few foods naturally contain vitamin D. Dietary sources include eggs from hens that have been fed vitamin D and fatty fish such as herrings, mackerel, sardines, and tuna. In the US, Canada, and many other countries the main source of dietary vitamin D is fortified milk and other foods. But these are relatively minor sources of vitamin D (7555).

Brief exposure to sunlight (about 25% of the amount of time it would take to cause light pinkness to the skin) is the most efficient way to get vitamin D (11935). Skin exposure to the sun provides as much as 80% to 90% of the body's vitamin D stores (7133). Full-body sun exposure can lead to the synthesis of as much as 10,000 units of vitamin D per day (6855). Vitamin D is stored in body fat for use during periods without sun exposure. Conversely, excessive sun exposure causes photodegradation of vitamin D produced in the skin, limiting the risk of vitamin D toxicity from such exposure (11936).

Vitamin D insufficiency is common in the northern latitudes such as Canada and the

northern half of the US (12995). Interestingly, vitamin D insufficiency also occurs in as many as 40% of older people even in sunny climates such as South Florida (15637). Prevalence of vitamin D insufficiency and deficiency among young, healthy people appears to be increasing, possibly because of excessive use of sunscreens (12995). Exposure to sunlight might not always be sufficient to cause vitamin D synthesis in the skin. Sunlight intensity is dependent on latitude, altitude, season, cloud cover, ozone levels and other factors. During winter in some northern latitudes (e.g., northern US and Canada), little, if any, vitamin D₃ is produced in the skin. For example, in Boston there is insufficient UV-B energy for vitamin D production in the skin for 4 months of the year. In Edmonton, the skin can't produce vitamin D for 5 months of the year (12998, 12999, 13000).

Underway submariners, who get no sunlight for extended periods of time, have lowered 25-hydroxyvitamin D levels and evidence of bone resorption and turnover, even when supplemented with 400 IU daily of cholecalciferol. The capacity of UV-B mediated vitamin D synthesis is huge. Just 6 days of casual sunlight exposure without sunscreen can make up for 49 days of no sunlight exposure (12998).

Skin pigmentation affects vitamin D synthesis and 25-hydroxyvitamin D levels. A light-skinned person in a bathing suit who is not tanned would receive about 10,000 to 20,000 IU of cholecalciferol from 10-12 minutes of peak July summer sun in Boston. For a darker-skinned person, such as Asian Indian, getting this dose of vitamin D could take perhaps 30 minutes of exposure, and, for a very darkly pigmented African American, it could require 120 minutes of exposure (12997). The skin pigment melanin competes with vitamin D precursors in the skin for photons from UV-B light (6857). When serum 25-hydroxyvitamin D levels are adjusted for percent body fat, Caucasian women have serum levels 1.3-1.9 times higher than African American women (16887). This also affects vitamin D in breast milk. For example, breast milk from African American women is generally lower in vitamin D content than that from Caucasian women (35 units/L compared with 68 units/L, respectively) (6857). African American infants who are exclusively breast-fed are therefore at risk for vitamin D deficiency and rickets, even if they live in sunny climates such as the southern US (6857).

Sun exposure is an easy, reliable way for most patients to get vitamin D. Exposure of the hands, face, arms, and legs to sunlight two to three times a week for the amount of time equal to about 25% of what it would take to develop a mild sunburn will cause the skin to produce adequate vitamin D. Exposure time will vary with skin type, season, time of day, etc (12992).

Vitamin D supplements may be needed by elderly people with limited sun exposure, people living in northern latitudes, dark-skinned African Americans, Asian Indians living in the western hemisphere, as well as people with gastrointestinal diseases leading to malabsorption of vitamin D from the diet (6855, 7133).

Vitamin D deficiency is particularly common in adults over age 50 years. More than 50% of North American women receiving therapy to prevent or treat osteoporosis have inadequate vitamin D stores (12996). Factors such as lack of exposure to sunlight, reduced skin synthesis of vitamin D, lower dietary intake, impaired intestinal absorption, chronic kidney disease, and reduced metabolism to active forms of vitamin D by the kidneys increase with aging (11919, 16883). Also, vitamin D receptors seem to decrease with age (11921). The risk for vitamin D deficiency in elderly adults (>65 years) is very high (12995, 12996). The risk for severe vitamin D deficiency is even greater with advanced age. A survey of 104 adults older than 98 years old found blood levels of vitamin D were detectable in only 5 adults. This correlates to a blood level of less than 2 ng/mL (16874).

Obese people (body mass index >30kg/m²) may have reduced serum vitamin D levels

and reduced bioavailability of vitamin D from both cutaneous synthesis and gastrointestinal absorption. In response to similar UV-B exposures, the increase in serum vitamin D levels can be 57% less in obese people than in those who are slim. The content of vitamin D precursors in the skin are similar in both groups, suggesting that vitamin D synthesis is not affected in obese people, but that vitamin D is sequestered into body fat, reducing its availability (6856).

The main function of vitamin D is to regulate serum calcium and phosphorus concentrations. Vitamin D enhances the efficiency of the intestinal absorption of calcium, primarily in the duodenum and jejunum, and phosphorus, particularly in the jejunum and ileum (7555). In the absence of adequate vitamin D, only 10% to 15% of calcium is absorbed and phosphorus absorption is only 60%. In the presence of vitamin D, calcium absorption increases to 30% to 40% and phosphorus absorption to 80% (16890). Vitamin D can increase serum calcium levels, but this effect is modest in healthy people in doses less than 1200 IU per day. If dietary intake of calcium is inadequate, calcitriol in combination with parathyroid hormone mobilizes calcium stores from bone. Calcitriol also appears to have effects in the brain, heart, pancreas, mononuclear cells, activated lymphocytes, and skin, but its exact physiologic role is unclear (7555).

The hydroxylation of vitamin D to calcitriol occurs in the kidneys. People with chronic renal failure may require forms of vitamin D such as calcitriol, dihydrotachysterol, or calcifediol that don't require renal hydroxylation (7555). In people with granulomatous disorders such as tuberculosis, sarcoidosis, and histoplasmosis, vitamin D metabolism is disturbed. Vitamin D is converted to calcitriol by activated macrophages trapped in the pulmonary alveoli and granulomatous inflammation, in addition to the kidneys. This may increase the risk of hypercalcemia (7555, 11881).

Since vitamin D is important for calcium homeostasis and for bone health, it is used to help prevent osteoporosis. Previously, researchers have suggested serum levels of 25-hydroxy-vitamin D (calcifediol) of at least 40 nmol/L for optimal bone health (6854). However, more recent research suggests serum levels of 70 to 80 nmol/L may be necessary for bone health (13276). When intake of calcium is low in healthy elderly women, 25-hydroxy-vitamin D (calcifediol) seems to be more biologically active and a more important determinant of gut calcium absorption than calcitriol (10141). Osteopenia in elderly men also seems to correlate with circulating levels of vitamin D and vitamin K (7132). Vitamin D deficiency causes muscle pain and proximal muscle weakness with symptoms such as sensation of heaviness in the legs, rapid fatigue, and problems with climbing stairs and getting up from a chair. Some preliminary clinical research suggests that people with low vitamin D levels (less than or equal to 20 ng/mL) have more osteoarthritis pain and disability than people with adequate vitamin D stores. Vitamin D deficiency also increases postural sway and affects psychomotor function (11922, 11923, 11924, 11925, 12491).

Vitamin D may prevent falls by increasing muscle strength and neuromuscular function in addition to strengthening bone. It seems to increase muscle protein synthesis, possibly by activating second messengers and phosphorylation (11919, 11922). Some evidence also shows that higher serum levels of vitamin D is associated with improved lower-extremity function in people aged 60 years or older (15636). The standard dose of 400 units that is found in most multivitamin tablets appears to be too low to prevent falls or reduce fracture risk, but the optimal dose is unknown (11926, 11927, 11928). Fractures were reduced in clinical trials using 700 to 800 units of vitamin D daily (980, 11930, 11931). Some research suggests that sufficient calcium intake along with vitamin D is necessary to prevent falls (11932).

Vitamin D also seems to have immunologic activity. In models of autoimmune disease, vitamin D seems to act as an immunosuppressant. This might explain why increased vitamin D intake is associated with a lower risk of rheumatoid arthritis (12206).

There is interest in using vitamin D for improving respiratory disorders such as bronchitis, chronic obstructive pulmonary disorder (COPD), and asthma. Epidemiological evidence suggests that 25-hydroxy vitamin D serum levels are associated with pulmonary function. People with higher levels seem to have greater pulmonary function as measured by FEV1 compared to people with lower levels. It is theorized that vitamin D might be involved in remodeling of lung tissue (14252, 17685). Vitamin D might also improve lung function by decreasing immune-mediated inflammation in the airway (14253).

Evidence from a population based study suggests patients with low 25-hydroxy vitamin D serum levels are 27% to 55% more likely to have upper respiratory tract infections compared to patients with normal levels (16830). It is not known if taking vitamin D supplements improves pulmonary function.

Vitamin D deficiency has been commonly reported in children with mild-to-moderate asthma and is also associated with increased risk of asthma exacerbations that are severe. Vitamin D receptor variants have been associated with asthma in some population studies. Additionally, population studies suggest that lower vitamin D levels are correlated with increased inhaled corticosteroid needs in children (17685). There is some epidemiological evidence that people with vitamin D deficiency might be at an increased risk of colon, breast, and prostate cancer (7555). Other evidence suggests that higher serum levels of vitamin D are associated with a decreased risk of cancer (14320). Some researchers think vitamin D might have antiproliferative effects in these cancers (6855). Prostate cancer has been associated with decreased sun exposure and vitamin D receptor activity (12994). Some evidence also suggests that vitamin D may play a role in the inhibition of cancer cell proliferation, differentiation, and apoptosis (16882).

Some evidence suggests vitamin D supplementation during infancy might prevent the development of type 1 diabetes later on in life. Type 1 diabetes is believed to be an autoimmune disease. Vitamin D supplementation might inhibit an autoimmune reaction that targets the beta cells of the pancreas (10139, 16886).

There is interest in using vitamin D to prevent and treat cardiovascular disease. Vitamin D is thought to play a role in cardiovascular disease by affecting inflammatory mediator such as tumor necrosis factor-alpha (TNF-alpha) and interleukin. Vitamin D might also decrease cardiac and vascular remodeling through suppression of the rennin gene and suppression of parathyroid hormone (14614, 16620, 16621, 16622). Some research shows that vitamin D supplementation might also suppress macrophage cholesterol uptake and decrease foam cell formation (16873).

Adverse Reactions:

Orally, vitamin D is well tolerated. Vitamin D intoxication can occur when vitamin D supplements are taken in excessive doses. Symptoms of vitamin D toxicity include hypercalcemia, azotemia, and anemia. Symptoms of hypercalcemia include weakness, fatigue, sleepiness, headache, loss of appetite, dry mouth, metallic taste, nausea, vomiting, abdominal cramps, constipation, diarrhea, dizziness, ringing in the ears, trouble walking, skin eruptions, hypotonia in infants, muscle pain, bone pain, and irritability. Advanced symptoms may include runny nose, itching, decreased libido, and kidney insufficiency due to precipitation of calcium phosphate in the tubules. Symptoms of renal impairment include frequency, nighttime awakening to urinate,

thirst, inability to concentrate urine, and proteinuria. Renal impairment is usually reversible with discontinuation of vitamin D supplements (10142). Other symptoms of vitamin D toxicity include osteoporosis in adults, decreased growth in children, weight loss, anemia, calcific conjunctivitis, photophobia, metastatic calcification, pancreatitis, generalized vascular calcification, and seizures. Rarely, people develop hypertension and psychosis. Lab values of urinary calcium, phosphate, albumin, blood urea nitrogen, serum cholesterol, aspartate aminotransferase, and alanine aminotransferase concentrations might increase (10142). Serum alkaline phosphatase concentrations usually decrease in vitamin D deficiency (7555).

There is some concern that administering vitamin D early in life could increase the risk of atopic conditions. Some population research suggests that administering vitamin D during the first year of life increases the risk of asthma, atopy, eczema, and allergic rhinitis later in life (17686). However, this is controversial. Other evidence suggests vitamin D deficiency might increase the risk of these conditions.

Interactions with Herbs & Supplements:

MAGNESIUM: The protein which transports calcium across the intestinal wall can also bind and transport magnesium. This protein is stimulated by vitamin D, which may therefore increase magnesium absorption (11595, 11598). In people with low vitamin D and magnesium levels, taking vitamin D may improve magnesium status (11599). In people with normal magnesium levels, this effect doesn't seem to be significant, possibly because urinary magnesium excretion also increases (11598).

Interactions with Drugs:

ALUMINUM

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Mild • Occurrence = Probable • Level of Evidence = B

The protein which transports calcium across the intestinal wall can also bind and transport aluminum. This protein is stimulated by vitamin D, which may therefore increase aluminum absorption (11595, 11597). This mechanism may contribute to increased aluminum levels and toxicity in people with renal failure, when they take vitamin D and aluminum-containing phosphate binders chronically (11529, 11596, 11597).

ATORVASTATIN (Lipitor)

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Mild • Occurrence = Probable • Level of Evidence = B

Atorvastatin is metabolized in the gut by cytochrome P450 3A4 (CYP 3A4) enzymes. Vitamin D is thought to induce this enzyme resulting in a reduced bioavailability of atorvastatin and other CYP3A4 substrates. Clinical research shows that taking two specific vitamin D products (Therapeutic-M, Goldline Laboratories and Oyster shell calcium with vitamin D, Major Pharmaceuticals) significantly reduces levels of atorvastatin and its active metabolites. Levels of all active components of atorvastatin decreased by 55% during vitamin D supplementation. Although atorvastatin levels decreased, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol levels did not substantially change (16828). Until more is known, advise patients to use vitamin D cautiously if they take atorvastatin.

CALCIPOTRIENE (Dovonex)

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Probable • Level of Evidence = D

Calcipotriene is a vitamin D analog used topically for psoriasis. It can be absorbed in sufficient amounts to cause systemic effects, including hypercalcemia (15).

Theoretically, combining calcipotriene with vitamin D supplements might increase the risk of hypercalcemia. Tell patients not to take vitamin D supplements if they are

taking calcipotriene.

CIMETIDINE (Tagamet)

Interaction Rating = **Minor** Be watchful with this combination.

Severity = Insignificant • Occurrence = Possible • Level of Evidence = B

Cimetidine inhibits an enzyme involved in conversion of vitamin D to its active form in the liver. However, it doesn't affect formation of active vitamin D metabolites in the kidneys. Clinically significant vitamin D depletion isn't likely, except in people with other risk factors such as liver or kidney disease (11531, 11532).

CYTOCHROME P450 3A4 (CYP 3A4) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Possible • Level of Evidence = B

Atorvastatin is metabolized in the gut by cytochrome P450 3A4 (CYP 3A4) enzymes. Vitamin D is thought to induce this enzyme resulting in a reduced bioavailability of atorvastatin and other CYP3A4 substrates. Clinical research shows that taking two specific vitamin D products (Therapeutic-M, Goldline Laboratories and Oyster shell calcium with vitamin D, Major Pharmaceuticals) significantly reduces levels of atorvastatin and its active metabolites. Levels of all active components of atorvastatin decreased by 55% during vitamin D supplementation. Although atorvastatin levels decreased, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol levels did not substantially change (16828). Until more is known, advise patients to use vitamin D cautiously if they take medications metabolized by CYP 3A4. Some drugs metabolized by CYP 3A4 include lovastatin (Mevacor), clarithromycin (Biaxin), cyclosporine (Neoral, Sandimmune), diltiazem (Cardizem), estrogens, indinavir (Crixivan), triazolam (Halcion), and others.

DIGOXIN (Lanoxin)

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = High • Occurrence = Possible • Level of Evidence = D

High doses of vitamin D can cause hypercalcemia. Hypercalcemia increases the risk of fatal cardiac arrhythmias with digoxin (15). Avoid vitamin D doses above the tolerable upper intake level (50 mcg or 2000 units/day for adults) and monitor serum calcium levels in people taking vitamin D and digoxin concurrently.

DILTIAZEM (Cardizem, Dilacor, Tiazac)

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Probable • Level of Evidence = B

High doses of vitamin D can cause hypercalcemia. Hypercalcemia can reduce the effectiveness of verapamil in atrial fibrillation (10574). Theoretically this could also occur with diltiazem. Avoid vitamin D doses above the tolerable upper intake level (50 mcg or 2000 units/day for adults) and monitor serum calcium levels in people taking vitamin D and diltiazem concurrently.

HEPARIN

Interaction Rating = **Minor** Be watchful with this combination.

Severity = Insignificant • Occurrence = Possible • Level of Evidence = D

Unfractionated heparin is associated with reduced bone density and osteoporotic fractures, especially when doses of 15,000 units/day or more are used for 3 months or longer (10577, 10594, 10595, 10596). This is primarily due to direct effects of heparin on bone (increased resorption and reduced bone formation), but metabolism of vitamin D to its active form is also reduced (10577, 10593, 10597). Although it's not clear whether vitamin D and calcium supplements prevent bone loss associated with heparin, recommend that people needing heparin therapy for several months maintain their recommended daily intakes of vitamin D and calcium, using supplements if necessary.

LOW MOLECULAR WEIGHT HEPARINS (LMWHs)

Interaction Rating = **Minor** Be watchful with this combination.

Severity = Insignificant • Occurrence = Possible • Level of Evidence = D

Reduced bone density has been reported with LMWHs, but probably to a lesser extent than with unfractionated heparin (10593, 10598, 10599, 11555). The effect is primarily due to direct effects of heparins on bone (increased resorption and reduced bone formation), but metabolism of vitamin D to its active form is also reduced (10577, 10593, 10597).

Although it's not clear whether vitamin D and calcium supplements prevent bone loss associated with LMWH, recommend that people needing therapy for several months maintain their recommended daily intakes of vitamin D and calcium, using supplements if necessary. LMWHs include enoxaparin (Lovenox), dalteparin (Fragmin), and tinzaparin (Innohep).

THIAZIDE DIURETICS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Probable • Level of Evidence = D

Thiazide diuretics decrease urinary calcium excretion, which could lead to hypercalcemia if vitamin D supplements are taken concurrently (3072, 11541). This has been reported in people being treated with vitamin D for hypoparathyroidism, and also in elderly people with normal parathyroid function who were taking a thiazide, vitamin D, and calcium-containing antacids daily (11539, 11540). Use combinations of thiazides and vitamin D with caution and monitor serum calcium levels. Thiazide diuretics include chlorothiazide (Diuril), hydrochlorothiazide (HydroDIURIL, Esidrix), indapamide (Lozol), metolazone (Zaroxolyn), chlorthalidone (Hygroton), etc.

VERAPAMIL (Calan, Covera, Isoptin, Verelan)

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Probable • Level of Evidence = B

Hypercalcemia due to high doses of vitamin D can reduce the effectiveness of verapamil in atrial fibrillation (10574). Avoid vitamin D doses above the tolerable upper intake level (50 mcg or 2000 units/day for adults) and monitor serum calcium levels in people taking vitamin D and verapamil concurrently.

Drug Influences on Nutrient Levels and Depletion:

CARBAMAZEPINE (Tegretol): Carbamazepine increases hepatic metabolism of vitamin D to inactive compounds, thereby reducing calcium absorption (2675, 4430, 4431). Hypocalcemia and osteomalacia have occurred, especially with prolonged therapy, concurrent use of other enzyme-inducing anticonvulsants, or when other risk factors for vitamin D deficiency are present (2675, 4475, 10578). Patients taking carbamazepine for 6 months or more may need vitamin D and calcium supplements. Doses of vitamin D needed vary from 400 to 4000 units/day; therefore serum calcium and vitamin D levels should be monitored in high-risk patients (10578).

CHOLESTYRAMINE (Questran, LoCholest, Prevalite): Cholestyramine can reduce absorption of vitamin D. Occasionally this leads to osteomalacia, usually in patients receiving doses of cholestyramine over 32 grams/day, or prolonged therapy over 2 years, and with additional risk factors such as ileal resection or primary biliary cirrhosis, which deplete the bile acids needed for vitamin D absorption (4458, 5655, 5809, 5838). Supplements of vitamin D, and sometimes calcium, are necessary in these patients. Use of cholestyramine (24 grams/day) for treatment of hyperlipidemia in otherwise healthy men doesn't seem to affect vitamin D and calcium levels, and supplements aren't necessary (2672).

COLESTIPOL (Colestid): Colestipol can reduce absorption of fat-soluble vitamins, including vitamin D. This doesn't seem to be clinically significant when up to 20 g/day is used for up to 2 years (4460, 4461). Monitor serum levels of calcium and vitamin D in people receiving very high doses of colestipol for several years and give supplements if necessary.

CORTICOSTEROIDS: Corticosteroids, in daily doses equivalent to 7.5 mg or more of prednisone, cause significant bone loss, osteoporosis and increased risk of fractures. The severity increases with duration of therapy. Although this is due mainly to disturbances in calcium homeostasis and bone formation, rather than vitamin D depletion, supplements of vitamin D are helpful to improve calcium absorption. Advise people taking prednisone 7.5 mg/day or higher (or equivalent doses of other corticosteroids) for 6 months or longer to maintain a daily calcium intake of 1500 mg/day, and

to take a supplement of 800 IU/day vitamin D. Serum calcium should be monitored regularly (1832).

MINERAL OIL: Mineral oil can reduce absorption of both vitamin D and calcium (4495). However, occasional or short-term use of mineral oil isn't likely to have a clinically significant effect.

ORLISTAT (Xenical, Alli): Orlistat decreases absorption of fat soluble vitamins including vitamin D, reducing plasma levels in some patients (1730, 9595, 10570). The manufacturer recommends that patients take a multivitamin supplement containing all the fat soluble vitamins, separating the dosing time by at least 2 hours from orlistat (1730).

PHENOBARBITAL: Phenobarbital increases hepatic metabolism of vitamin D to inactive compounds, thereby reducing calcium absorption (2675, 4430, 4431). Hypocalcemia and osteomalacia have occurred, especially with prolonged therapy, concurrent use of other enzyme-inducing anticonvulsants, or when other risk factors for vitamin D deficiency are present (2675, 4475, 10578). Patients taking phenobarbital for 6 months or more may need vitamin D and calcium supplements. Doses of vitamin D needed vary from 400-4000 units/day; therefore serum calcium and vitamin D levels should be monitored in high-risk patients (10578).

PHENYTOIN (Dilantin), FOSPHENYTOIN (Cerebyx): phenytoin increases hepatic metabolism of vitamin D to inactive compounds, thereby reducing calcium absorption (2675, 4430, 4431). Hypocalcemia and osteomalacia have occurred, especially with prolonged therapy, concurrent use of other enzyme-inducing anticonvulsants, or when other risk factors for vitamin D deficiency are present (2675, 4475, 10578). Patients taking phenytoin for 6 months or more may need vitamin D and calcium supplements. Doses of vitamin D needed vary from 400-4000 units/day; therefore serum calcium and vitamin D levels should be monitored in high-risk patients (10578).

RIFAMPIN (rifampicin, Rifadin, Rimactane): Rifampin increases hepatic metabolism of 25-hydroxy-vitamin D, reducing its plasma levels (11561, 11562, 11563). This can contribute to osteomalacia after prolonged therapy (>1 year), especially if vitamin D intake is low (11562, 11564). Monitor serum levels of calcium and vitamin D in people taking rifampin for prolonged periods and give supplements as necessary. If isoniazid (INH, Nydrazid) is taken concurrently with rifampin there doesn't seem to be any change in vitamin D status (11561, 11563). Possibly this is because the enzyme-inducing effects on rifampin are canceled out by the enzyme-inhibiting effects of isoniazid (11563, 11565).

STIMULANT LAXATIVES: Prolonged use of high doses of stimulant laxatives can reduce dietary vitamin D and calcium absorption, leading to hypocalcemia and osteomalacia (11530). Advise patients to limit stimulant laxatives to short-term use of recommended doses. Some stimulant laxatives include senna (Senokot), bisacodyl (Dulcolax), and others.

SUNSCREENS: Frequent and extensive application of sunscreens can reduce vitamin D synthesis in the skin and plasma levels (11507, 11508, 11509). There is increasing concern that overuse of sunscreen can contribute to vitamin D deficiency and increased risk of some kinds of cancer (12992, 12993). Tell patients brief sun exposure is not likely dangerous and helps maintain adequate vitamin D levels. For longer exposure than a "dose" of dermal vitamin D, recommend use of a sunscreen with an SPF 15 or greater to protect the skin. Advise people to maintain the recommended dietary intake of vitamin D. Consider supplements for people with minimal sun exposure and poor dietary intake (12992).

Interactions with Foods:

None known.

Interactions with Lab Tests:

None known.

Interactions with Diseases or Conditions:

ARTERIOSCLEROSIS: Hypercalcemia can contribute to arteriosclerosis, particularly in patients with kidney disease. Use supplemental vitamin D cautiously (11815, 11816).

HISTOPLASMOSIS: Vitamin D may increase calcium levels in people with histoplasmosis. The metabolism to calcitriol is increased in people with histoplasmosis, which may cause hypercalcemia and complications such as kidney stones and calcified tissue. Use supplemental vitamin D cautiously (11881).

HYPERCALCEMIA: Vitamin D supplements may worsen hypercalcemia (11815).

HYPERPARATHYROIDISM: Vitamin D may increase calcium levels in people with hyperparathyroidism. Use supplemental vitamin D cautiously (11815).

LYMPHOMA: Vitamin D may increase calcium levels in people with lymphoma. In some kinds of lymphoma, vitamin D is more readily converted to calcitriol and may result in hypercalcemia and complications such as kidney stones and calcified tissue. Use supplemental vitamin D cautiously (11815, 11881).

RENAL DISEASE: Vitamin D may increase calcium levels and increase the risk of arteriosclerosis in renal failure. This must be balanced with the need to prevent renal osteodystrophy. Monitor calcium levels carefully (11816).

SARCOIDOSIS: Vitamin D may increase calcium levels in people with sarcoidosis. The metabolism to calcitriol is increased in people with sarcoidosis, which may cause hypercalcemia and complications such as kidney stones and calcified tissue. Use supplemental vitamin D cautiously (11881).

TUBERCULOSIS: Vitamin D may increase calcium levels in people with tuberculosis. The metabolism to calcitriol is increased in people with tuberculosis, which may cause hypercalcemia and complications such as kidney stones and calcified tissue. Use supplemental vitamin D cautiously (11881).

Dosage/Administration:

ORAL: For treating vitamin D deficiency, 50,000 IU/week orally for 6-12 weeks has been used for adults (17476); however, some patients require higher doses for longer periods of time to maintain adequate 25-hydroxyvitamin D levels. Optimal blood levels of 25-hydroxyvitamin D for maintaining bone density is 30-100 ng/mL.

For preventing osteoporosis and fractures, 400-1000 IU daily has been used (980, 1836, 6362, 8818, 10140, 10932, 12926, 12930, 12933, 12934, 12952) (13276, 14282, 15633). Some experts now recommend higher doses up to 2000 IU daily for preventing osteoporosis (17475, 17476). Maintenance doses of 14,000 IU once weekly or 50,000 IU once monthly are also sometimes used (17476). Some patients need even higher doses to maintain adequate vitamin D levels. Optimal blood levels of 25-hydroxyvitamin D for maintaining bone density is 30-100 ng/mL (17476).

For preventing falls, 800-1000 IU/day has been used in combination with calcium 1000-1200 mg/day (11939, 15606, 16275).

For preventing multiple sclerosis (MS), long-term consumption of at least 400 IU per day, mainly in the form of a multivitamin supplement, has been used (11356).

For hyperlipidemia, vitamin D 400 IU plus calcium 1200 mg daily has been used (15601).

For preventing all cancer types, calcium 1400-1500 mg/day plus vitamin D3 (cholecalciferol) 1100 IU/day in postmenopausal women has been used (15629).

Another trial on colorectal cancer in postmenopausal women has used calcium 1000 mg/day plus vitamin D 400 IU/day (14290); however, findings in this trial were not positive.

For myalgia associated with statin therapy, ergocalciferol 50,000 IU once a week or 400 IU daily of ergocalciferol or cholecalciferol have been used (16831).

For influenza, vitamin D (cholecalciferol) 1200 IU daily has been used (17486).

INTRAMUSCULAR: For vitamin D deficiency, a single intramuscular injection of 600,000 IU (15 mg) (Arachitol, Solvay Pharma) of vitamin D has been used (16888).

Most vitamin D supplements contain the equivalent of 400 IU (10 mcg) vitamin D.

The Institute of Medicine publishes a recommended daily allowance (RDA) for

vitamin D which is an estimate of the intake level necessary to meet the requirements of nearly all healthy individuals in the population. The current RDA was set in 2010. The RDA varies based on age as follows: 1-70 years of age, 600 IU daily; 71 years and older, 800 IU daily; pregnant and lactating women, 600 IU daily. For infants ages 0-12 months, an adequate intake (AI) level of 400 IU is recommended (17506). The current RDA assumes that ergocalciferol and cholecalciferol are equivalent; however, some evidence indicates that ergocalciferol is less than one third as potent as cholecalciferol. Therefore, many experts now recommend using vitamin D supplements containing cholecalciferol in order to meet these intake levels (15263, 15264).

Several other organizations also publish recommended intake levels. Many of these recommendations are higher than the RDA set by the Institute of Medicine. In 2008, the American Academy of Pediatrics increased the recommended minimum daily intake of vitamin D to 400 IU daily for all infants and children, including adolescents (16614). Advise parents not to use vitamin D liquids dosed as 400 IU/drop. Giving one dropperful or mL by mistake can deliver 10,000 IU/day. The US Food and Drug Administration (FDA) will force companies to provide no more than 400 IU per dropperful.

Some authorities recommend 1000 units/day for older adults who are not exposed to sunlight (11933). The National Osteoporosis Foundation recommends vitamin D 400 IU to 800 IU daily for adults under age 50, and 800 IU to 1000 IU daily for older adults (16120). The North American Menopause Society recommends 700 IU to 800 IU daily for women at risk of deficiency due to low sun (e.g., homebound, northern latitude) exposure (16121). Similarly, guidelines from the Osteoporosis Society of Canada recommend vitamin D 400 IU per day for people up to age 50, and 800 IU per day for people over 50 (16122). Osteoporosis Canada now recommends 400-1000 IU daily for adults under the age of 50 years and 800-2000 IU daily for adults over the age of 50 years (17475, 17476). The Canadian Cancer Society recommends 1000 IU/day during the fall and winter for adults in Canada. For those with a higher risk of having low vitamin D levels, this dose should be taken year round. This includes people who have dark skin, usually wear clothing that covers most of their skin, and people who are older or who don't go outside often (15632).

Editor's Comments:

Canada recognizes the importance of vitamin D in the prevention of osteoporosis in its health claim for foods that contain calcium: "A healthy diet with adequate calcium and vitamin D, and regular physical activity, help to achieve strong bones and may reduce the risk of osteoporosis" (11940). The US version of this osteoporosis health claim does not yet include vitamin D.

This monograph was last reviewed on 02/03/2012 and last updated on 02/03/2012. Monographs are reviewed and/or updated multiple times per month and at least once per year. If you have comments or suggestions on something that should be reviewed or included, please [tell the editors](#). For details about our evidence-based approach, see our [Editorial Principles and Process](#).

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