

Vitamin D (Calciferol)

Nutrient Names: Vitamin D, calciferol.

Synonyms: 1,25-Dihydroxyvitamin D, calciferol, calcipotriol, cholecalciferol (vitamin D₃), ergocalciferol (vitamin D₂), irradiated ergocalciferol, ergosterol (provitamin D₂), activated/irradiated ergosterol (vitamin D₂).

Related Substance: Calcitriol is also the name of a drug that is the active (1,25-dihydroxycholecalciferol) form of vitamin D.

Summary

Drug/Class Interaction Type	Mechanism and Significance	Management
Allopurinol ⊕⊕	Allopurinol may elevate serum concentrations of 1,25(OH) ₂ -vitamin D ₃ by reducing uric acid's inhibition of 1-hydroxylase activity.	Assess vitamin D status. Allopurinol may increase 1,25(OH) ₂ D levels, especially with supplementation.
Androgen-deprivation therapy (ADT) ☼/⊕⊕	Concomitant vitamin D and calcium can counter skeletal impact of deficiency patterns associated with prostate cancer treatment, decreased sex hormone levels, and ADT, especially when used with bisphosphonates. Consensus of evidence is emerging for this clinically significant, supportive interaction, as are clinical guidelines.	Coadminister vitamin D and calcium and monitor bone and D status. Promote sunlight exposure and exercise.
Anticonvulsant medications ≈≈≈/◇/☼	Phenytoin and phenobarbital accelerate vitamin D metabolism in liver (CYP450 induction) and may reduce serum levels of 25(OH)D. Thus, anticonvulsants may impair mineralization, leading to increased risk of bone loss, osteoporosis, osteomalacia, rickets, and fractures. Coadministration of "high-dose" vitamin D can mitigate drug-induced vitamin D depletion and related bone loss.	Coadminister vitamin D and calcium. Monitor serum 25-OHD and bone status. Promote sunlight exposure and weight-bearing exercise.
Bisphosphonates ⊕⊕⊕	Synergistic interaction; vitamin D assists calcium absorption, and both enable bisphosphonates in maintaining bone mineralization, including with hormone replacement therapy (HRT).	Coadminister vitamin D; administer calcium but separate intake from bisphosphonates. Promote appropriate sunlight exposure and weight-bearing exercise.
Calcitriol Vitamin D analogs XX/XXX/◇◇◇	Additive effect from concurrent use would increase risk of vitamin D toxicity, especially since 1,25(OH) ₂ D and analogs bypass renal feedback controls.	Caution; generally avoid. Possible value in coadministration (e.g., renal disease) with monitoring.
Cholestyramine Colestipol Bile acid sequestrants ≈≈≈/◇	Bile acid sequestrants decrease lipid digestion and absorption and thereby reduce absorption of vitamin D and fat-soluble nutrients. Risk of deficiency and sequelae.	Supplement vitamin D. Promote sunlight exposure and weight-bearing exercise.
Cimetidine Histamine (H ₂) receptor antagonists ≈≈≈/◇	Cimetidine may inhibit action of vitamin D hydroxylase and could reduce hepatic activation of vitamin D through hydroxylation. Possible risk of deficiency.	Monitor 25(OH)D. Compensatory supplementation may be appropriate.
Corticosteroids, oral ≈≈≈/◇≈≈/◇	Oral corticosteroids reduce calcium absorption and may increase excretion while decreasing vitamin D availability and lowering serum levels. Increased risk of bone loss, osteoporosis, and fractures with long-term oral steroid use.	Supplement vitamin D and calcium. Monitor bone and 25(OH)D status with steroid use > 1 month. Promote sunlight exposure and exercise.
Estrogens/progestins Hormone replacement therapy (HRT) ⊕⊕/XX	Synergistic interaction, especially with osteoporosis. Vitamin D assists calcium absorption, and both enable estrogen in inhibiting osteoclastic activity and bone resorption and maintaining bone mineralization. Progestins may counter benefit.	Coadminister vitamin D and calcium (separate intake), possibly bisphosphonates. Monitor bone, 25(OH)D, and HDL. Promote sunlight and exercise.
Heparin, unfractionated ◇≈≈/≈≈	Heparin therapy is associated with bone loss. Heparin may also inhibit formation of 1,25(OH) ₂ D by kidneys. Risks of bone loss and associated nutrient depletion with extended heparin use are significant. Limited evidence supporting protective effect of oral vitamin D.	Coadminister vitamin D and calcium, possibly as hydroxyapatite. Monitor bone and 1,25(OH) ₂ status with heparin use > 1 month.
Isoniazid (INH) ≈≈	Isoniazid can lower levels of both activated vitamin D and calcium levels; can also inhibit hepatic mixed-function oxidase activity, hepatic 25-hydroxylase and renal 1α-hydroxylase and reduce corresponding vitamin D metabolites. Drug-induced vitamin D deficiency can produce hypocalcemia and elevate parathyroid hormone. Nutrient support unlikely to interfere with drug's therapeutic activity.	Supplement vitamin D and calcium when INH used for > 1 month. Promote sunlight exposure. Monitor 25(OH)D and bone status.
Ketoconazole ⊕X	Ketoconazole inhibits P450 enzymes to block adrenal steroidogenesis; also inhibits both synthesis of activated vitamin D and its metabolism by 1 alpha-hydroxylase and 24-hydroxylase, thus maintaining 1,25(OH) ₂ -vitamin D levels if it is supplemented. Ketoconazole reduces calcium (and 1,25-D) in hypercalcemia and sarcoidosis.	Monitor for vitamin D deficiency with long-term use. Calcitriol may be necessary. Half-life of administered calcitriol prolonged in presence of ketoconazole.
Neomycin ≈≈≈/◇	Long-term use of neomycin decreases absorption and/or increases elimination of many nutrients, including vitamin D. Risk of deficiency and sequelae.	Supplement multivitamin-mineral with extended use.

Continued

Summary

Drug/Class Interaction Type	Mechanism and Significance	Management
Orlistat ≈≈≈	Orlistat binds fat to prevent absorption and can interfere with absorption of vitamin D and other fat-soluble nutrients. Possible risk of significant deficiency.	Supplement multivitamin with extended use. Separate intake timing.
Raloxifene ⊕⊕	Synergistic interaction; vitamin D assists calcium absorption, and both enable raloxifene in inhibiting bone resorption.	Coadminister D ₃ plus calcium. Monitor 25(OH)D and bone status. Promote sunlight exposure and exercise.
Rifampin ≈≈/◇≈≈	Rifampin induces cytochrome P450, resulting in decreased plasma levels of 25-hydroxycholecalciferol (25-OHD). Risk of significant deficiency uncertain.	Supplement D ₃ when rifampin > 1 month. Monitor 25(OH)D status.
Thiazide diuretics ◇◇/XXX	Thiazides reduce calcium excretion and could potentially lead to hypercalcemia (rare) and changes in vitamin D metabolism. Significance of interaction uncertain.	Monitor serum calcium.
Thioridazine XXX	Cholecalciferol inhibits hepatic cytochrome P2D6 and may decrease the metabolism of thioridazine. Concurrent use might increase activity and adverse effects of drug.	Monitor vitamin D status; supplementation may be appropriate but only under close supervision. Consider alternatives to thioridazine.
Verapamil Calcium channel blockers XXX/◇◇◇/◇◇◇	Vitamin D can increase calcium availability, which opposes verapamil's activity as calcium antagonist. Excess vitamin D might theoretically contribute to hypercalcemia on rare occasions, which in turn might theoretically precipitate cardiac arrhythmia in patients taking verapamil. Minimal evidence and low probability but potentially severe.	Concurrent supplementation with vitamin D (and calcium) may be appropriate but only under close supervision. Consider bone support needs.

NUTRIENT DESCRIPTION

Chemistry and Forms

Vitamin D is the generic term for compounds that exhibit the biological activity of calciferol: vitamin D₂ (ergocalciferol), vitamin D₃ (cholecalciferol), 1α(OH)D₃ (alfacalcidol), 25(OH)D₃ (calcifediol, calcidiol), 1,25(OH)₂D₃ (calcitriol), and dihydrotachysterol.

Physiology and Function

Vitamin D functions as both a fat-soluble vitamin and a hormone. From dietary sources, vitamin D is absorbed from the small intestine in the presence of bile and is transported into the circulation via the lymph in chylomicrons (similar to vitamin A transport). Vitamin D can also be synthesized in the skin as a result of direct exposure to the ultraviolet light in sunlight (UVB radiation) through the conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D₃). This ability of animals to produce vitamin D from a cholesterol derivative makes the nutrient a “conditionally essential” vitamin. On entering the circulation from either the diet or the skin, vitamin D₃ is bound to the vitamin D-binding protein and transported to the liver. Two successive hydroxylations of vitamin D, first in the liver (to 25-hydroxycholecalciferol) and then in the kidneys, produce the hormonally active form, calcitriol, or 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D₃), in coordination with the parathyroid glands and calcium-sensitive parathyroid hormone (PTH, parathormone) secretion.

Calcitriol binds to the *vitamin D receptor* (VDR), a nuclear transcription factor that regulates gene expression. When the calcitriol/VDR complex subsequently combines with the *retinoic acid X receptor* (RXR), the resulting VDR/RXR heterodimer can interact with the vitamin D-responsive elements (VDREs) within the DNA. This interaction between the VDR/RXR heterodimer and a VDRE alters the rate of transcription of a related gene and thereby regulates the activity of vitamin D-dependent calcium transporters in the small intestine, osteoblasts in bone, and the 1-hydroxylase enzyme in the kidneys. Defects in the vitamin D receptor lead to hypocalcemic vitamin D-resistant rickets, congenital total lipodystrophy, and persistent müllerian duct syndrome. Research suggests that bone may be more responsive to

exercise in some genotypes of VDR than in others,¹ and that gene-environment interactions such as leisure physical activity and VDR genotype may play a role in maintaining the bone mineral density (BMD) at the lumbar spine in active postmenopausal women, especially in older active women.²

The vitamin D endocrine system is responsible for maintaining tight regulation of serum calcium levels within the narrow range critical to bone metabolism and healthy functioning of the nervous system. Calcitriol mediates the intestinal absorption and blood levels of calcium and phosphorus. It facilitates mineral deposition into bone, modulates bone mineralization and demineralization, and enhances muscle strength and balance. Vitamin D is necessary to calcium absorption and increases the absorption of calcium from the intestine (by stimulating the synthesis of calcium-binding protein and the epithelial calcium channel) and maintains serum calcium levels in the normal range; thus increasing resorption of calcium from bone as well as facilitating calcium storage in the bones. Consequently, even though it initially causes bone resorption, the net effect is to increase calcium deposition in the bone. In addition to promoting calcium absorption, calcitriol mediates the intestinal absorption of phosphorus, possibly magnesium and zinc as well, and may promote renal tubule phosphate resorption. Vitamin D is stored in body fat.

Vitamin D also plays many important roles in hormonal regulation and immune function. It helps maintain adequate blood levels of insulin and may assist the metabolism of sugar. Vitamin D may also assist healthy thyroid function, and the active form of vitamin D₃ may have a mechanism of action similar to thyroid hormone. Vitamin D and VDRs participate in the regulation of cell growth and development, particularly white blood cells and epithelial cells. In particular, the presence of VDRs in T lymphocytes suggests that vitamin D facilitates the development, activity, and response of T cells against antigens (and in autoimmune disorders).

NUTRIENT IN CLINICAL PRACTICE

Known or Potential Therapeutic Uses

Vitamin D is used to prevent osteoporosis and osteoporotic fractures, and intake is associated with reduced risk of breast cancer, colorectal cancer, prostate cancer, as well as cancers of

the lung, skin (melanoma), colon, and bone. Administration of vitamin D in conjunction with bisphosphonate therapy (e.g., alendronate, risedronate, or etidronate) or exogenous hormone therapy (e.g., HRT) may enhance clinical outcomes in preventing and treating osteoporosis. A range of autoimmune diseases, particularly type 1 diabetes mellitus, rheumatoid arthritis, and multiple sclerosis, may be responsive to integrative therapeutics employing vitamin D, especially when they involve a VDR gene polymorphism. Calcitriol, the active metabolite of vitamin D, has been found to inhibit the growth of human prostate cancer cells *in vitro*; however, findings from preliminary human trials have been disappointing for its use (or that of analogs) as part of innovative protocols in the treatment of hormone-refractory prostate cancer.

Historical/Ethnomedicine Precedent

The physiological parameters of vitamin D may be premised on the ancient origins of humans in equatorial Africa. The high level of exposure to sun inherent to such an interaction with the environment may play a fundamental role in the high susceptibility for insufficiency or deficiency among modern humans less exposed to the sun, especially for dark-skinned individuals, because melanin acts as an ultraviolet absorber.

Possible Uses

Atherosclerosis, autoimmune diseases, breast cancer, burns, cancer prevention, celiac disease, digestive system cancers (oral, esophageal, stomach, pancreas, colorectal; risk reduction, especially in individuals with dark skin), Crohn's disease, depression (particularly seasonal affective disorder), diabetes mellitus, epilepsy, falls (prevention, especially in the elderly), fractures (especially in the elderly), hearing loss, hyperparathyroidism (secondary), hypertension, hypoparathyroidism, migraine headaches, multiple sclerosis, obesity, osteoarthritis, osteomalacia, osteoporosis, prevention of vitamin D deficiency, prostate cancer, psoriasis, rheumatoid arthritis (risk reduction), rickets, scleroderma, skin cancer (risk reduction), tuberculosis.

Deficiency Symptoms

Rickets, osteomalacia, osteoporosis, and fracture risk remain the most obvious and well-known outcomes associated with vitamin D deficiency. Researchers have increasingly expressed concern that the low levels of vitamin D found in a large percentage of Americans and Europeans may be associated with increased risk of a range of conditions, including cancer, heart disease, hypertension, diabetes, multiple sclerosis, and diminished immune status. The classic groups known for increased risk of deficiency are breast-fed infants, individuals on vegetarian diets, the elderly, individuals with fat malabsorption or chronic kidney disease, and individuals with compromised sun exposure due to lifestyle, climate, season, or cultural practices. Other significant etiologies include alcoholism, burns (and burn scarring), Crohn's disease, Cushing's disease, dark skin, decreased consumption of vitamin D, hypothyroidism, anticonvulsant drug therapy, kidney or liver disease, malabsorption (as in celiac disease or after intestinal surgery), ulcerative colitis, and vitamin D-resistant rickets. Vitamin D receptor polymorphic alleles have been linked to diabetes mellitus and colon cancer.^{3,4} Low dietary calcium intake may enhance the phenotypic expression of VDR gene polymorphisms.⁵

Awareness of previously unrecognized vitamin D deficiency and its implications in long-term pathological processes has been growing in recent years.^{6,7} Chapuy et al.⁸ (1997) reported that one of seven adults may be deficient in vitamin D. Similarly, a study in 1998 by Thomas et al.⁹ found that 37% of the total group surveyed were deficient in vitamin D, even though their reported diets should have provided the currently recommended levels of vitamin. This study also found that 42% of hospitalized patients under age 65 were deficient in vitamin D. Overall, vitamin D inadequacy has been reported in up to 57% of general medicine inpatients in the United States.¹⁰ Spanish researchers found that healthy postmenopausal women in modern societies have an extremely high prevalence of vitamin D deficiency.¹¹ Likewise, young adults exhibit an unexpectedly high incidence of vitamin D insufficiency.¹² Vitamin D deficiencies may also raise the risk of prostate cancer by disrupting the relationship between androgens and VDR in prostate cells.¹³

Dietary Sources

Cod liver oil, oily cold-water fish (salmon, mackerel, herring), butter, egg yolks, vitamin D-fortified milk, and orange juice.

Most vitamin D in humans is derived from endogenous synthesis subsequent to sun exposure rather than from dietary sources. Vitamin D is found primarily in foods of animal origin, unless they are fortified. Cod liver oil is considered an excellent dietary source. Vegetables are usually low in vitamin D, although mushrooms, if irradiated, can be a significant source of vitamin D. Milk used to make cheese or yogurt is usually not fortified with vitamin D. Human milk contains the 25-hydroxycholecalciferol form of D, possibly to compensate for the limited ability of the liver in infants to achieve the first hydroxylation of cholecalciferol. The vitamin D content in human milk varies with maternal sun exposure and vitamin D intake.

Sunshine

With exposure to ultraviolet light, the skin synthesizes vitamin D. It is estimated that 20 minutes, with face and arms exposed, will stimulate about 600 to 1000 IU per day, during spring, summer, and fall in temperate regions, and year-round in tropical and subtropical regions. Enough sun or UVB exposure to produce minimal skin erythema (known as the *minimal erythemic dose*) can produce 10,000 to 20,000 IU in about an hour. Adequate amounts of vitamin D can theoretically be synthesized and stored in fat to carry an individual through the winter. In temperate latitudes, above 35° to 50°, a minimum of 15 minutes of sun exposure on the arms, face, and hands three times per week in the morning or late afternoon during the spring, summer, and fall is needed to avoid vitamin D deficiency at the end of winter. However, research indicates that, in actuality, many individuals in higher latitudes, especially with seasonal clothing, overcast climates, and minimal time outdoors, do not receive adequate sun exposure to avoid compromised vitamin D status. Sun exposure with sunscreen significantly prevents skin synthesis of vitamin D.

Dosage Forms Available

Capsules, injection (IM), liquid, tablets. Intramuscular (IM) form is not available in the United States.

Oral dosing (with meals) is preferred, but malabsorption associated with gastrointestinal, liver, or biliary disease may necessitate IM injection.

Nutrient Preparations Available

Cholecalciferol (vitamin D₃) is more potent and bioavailable than ergocalciferol (D₂).

*Dosage Range***Adult**

Dietary: The adequate intake of vitamin D (cholecalciferol, or vitamin D₃) is 5 µg (200 IU) per day for adults age 19 to 50 years, 10 µg (400 IU) for adults age 51 to 70 years, and 15 µg (600 IU) for adults 71 years and older.

Supplemental/Maintenance: 10 µg (400 IU) per day. However, in some cases this may be unnecessary, given consistent adequate direct exposure to the sun, usually 20 minutes per day. Supplement with cod liver oil if 25(OH)D levels are low (1 tsp per 50 pounds of body weight). One tablespoon of cod liver oil provides approximately 1200 IU (30 µg) of vitamin D₃.

A dose of 20 µg (800 IU) per day for individuals, especially the elderly, not adequately exposed to sunlight or living in farther northern or southern latitudes.

Pharmacological/Therapeutic: 800 to 2000 IU per day, including dietary sources, under supervision of a physician or health care professional experienced in nutritional therapeutics.^{14,15} Dosages used in clinical studies range from 5 µg (200 IU) to 250 µg (10,000 IU) daily. Significantly higher doses are often used in the treatment of secondary hypoparathyroidism, vitamin D-resistant rickets, nutritional rickets and osteomalacia, and familial hypophosphatemia.

Toxic: The current official tolerable upper intake level (UL) is 50 µg (2000 IU) per day. However, many experts in the field strongly support raising the UL to at least 4000 IU, and 10,000 IU may be tolerable for most individuals, but such a daily dose should be medically monitored.

Adverse effects have been reported at concentrations ranging from 250 to 1250 µg (10,000-50,000 IU) per day.

Pediatric (<18 years)

Dietary: The adequate intake (AI) of vitamin D (cholecalciferol, or vitamin D₃) is 5 µg (200 IU) per day for infants and children up to 18 years.

Supplemental/Maintenance: One teaspoon of cod liver oil per 50 lb/wt. Sun exposure of 20 minutes daily is adequate and preferable. Do not give cod liver oil when sun exposure is being implemented.

Pharmacological/Therapeutic

Premature infants: 10 to 20 µg (400-800 units) per day, up to 750 µg (30,000 IU) per day.

Infants and healthy children: 10 µg (400 IU) per day.

Significantly higher doses are often used in the treatment of hypoparathyroidism, nutritional rickets and osteomalacia, vitamin D-resistant rickets, and familial hypophosphatemia. Vitamin D receptor defects, specifically tissue resistance to vitamin D, or vitamin D-dependent rickets (VDDR), are usually treated with 20 µg/day of the bioactive form, calcitriol, or 5 mg/day of the dietary form, vitamin D₂, plus oral calcium and phosphate.¹⁶

Toxic: UL for infants (0-12 months) is 25 µg (1000 IU) per day and for children (1-18 years) is 50 µg (2000 IU) per day.

Note: Requirements depend on the exposure of a person's skin to ultraviolet radiation. The intensity of exposure is also a factor. The latitude determines how much exposure to sunlight

the person requires to synthesize adequate levels of vitamin D. Pollution, clouds, and skin color also affect an individual's ability to produce vitamin D. The darker the skin, the less vitamin D will be produced (up to 95% blocked). However, with longer exposure times, even with the darkest skin color, sufficient levels of vitamin D are produced. Glass and topical sunscreens block UV light.

Laboratory Values

Laboratory assessment of vitamin D status has been in a state of controversy and evolution in recent years, particularly since the effects of mild vitamin D deficiency or insufficiency have become more widely recognized.

Plasma 25(OH)-Vitamin D

This assay reflects body reserves. Plasma levels less than 25 nmol/L indicate deficiency.

However, results from laboratories doing 25-hydroxyvitamin D (25-OHD) tests vary widely.¹⁷ Reference ranges from most labs are too low. Optimal serum levels of 25-OHD to avoid increases in PTH are at least 20 ng/mL,¹⁸ but may actually be in the range of 45 to 55 ng/mL (115-140 nmol/L). Heaney et al.^{19,20} suggest that the appropriate serum 25-OHD level is 32 ng/mL.⁸ Concurrent parathyroid tests (PTH) may elucidate equivocal laboratory findings because one could expect a high PTH if there is a low vitamin D concentration in the blood.

Plasma 1,25(OH)₂-Vitamin D

This assay measures the active form of the vitamin. As 25-OHD levels drop, PTH secretion increases (secondary hyperparathyroidism), which maintains the 1,25(OH)₂-vitamin D level in the normal range. For this reason, measuring the 25-OHD level is necessary to diagnose vitamin D deficiency or insufficiency. Normal 1,25(OH)₂D levels are 48 to 100 pmol/L.

Also, measure serum calcium, blood urea nitrogen (BUN), and phosphorus every 1 to 2 weeks; and monitor bone density regularly until stabilized.

Serum calcium concentration times phosphorus concentration should not exceed 70 mg/dL to avoid ectopic calcification; ergocalciferol levels: 10 to 60 ng/mL; serum calcium: 9 to 10 mg/dL; phosphorus: 2.5 to 5.0 mg/dL.

SAFETY PROFILE*Overview*

Vitamin D is generally well tolerated, and excessive doses from sunlight exposure or dietary source are considered highly improbable, if not impossible. Its UL of 50 µg (2000 IU) per day reflects that vitamin D has long been considered the most likely of all vitamin supplements to cause toxicity. Although a revised consensus has developed in recent years among researchers and some clinicians, regulatory and institutional guidelines are only gradually beginning to respond to and integrate the new data into their recommendations.

Adverse effects have been reported at concentrations ranging from 250 to 1250 µg/daily.²¹ Hypervitaminosis D has generally been associated with intake of 625 to 1500 µg (25,000-60,000 IU) daily for 1 to 4 months, or several years of vitamin D supplementation at 250 to 1250 µg (10,000-50,000 IU) daily, and has never been associated with sun exposure. Published case reports of vitamin D toxicity with hypercalcemia, for which the 25(OH)D concentration

and vitamin D dose are known, all involve intake of at least 1000 µg (40,000 IU) per day, and only one case occurred at a level of intake under 40,000 IU/day.¹⁴

However, emerging evidence and the opinions of many vitamin D researchers now suggest that the daily value (DV) of 400 IU for vitamin D, which was based on the amount necessary to prevent rickets in infants (initially given as 5 mL of cod liver oil 100 years ago) is an order of magnitude below the amount necessary for older adults, and those not exposed to sun without sunscreen on a regular basis, to achieve and maintain blood levels of vitamin D that are optimum for bone health and cancer prevention.^{15,22-33} “Estimates of the population distribution of serum 25(OH)D values, coupled with available dose-response data, indicate that it would require input of an additional 2600 IU/d (65 mcg/d) of oral vitamin D₃ to ensure that 97.5% of older women have 25(OH)D values at or above desirable levels.”³⁴ Absent lymphoma or granulomatous disease, which can cause vitamin D sensitivity, it appears that long-term ingestion of greater than 10,000 IU/day is necessary to cause vitamin D toxicity and hypercalcemia.

Nutrient Adverse Effects

General Adverse Effects

Excessive levels of vitamin D intake over an extended period can lead to headaches, kidney stones, and weight loss. Less common symptoms include diarrhea, increased thirst, increased urination, irritability, and failure to gain weight in children. More extreme consequences include blindness, deafness, and potentially death. Elevated vitamin D levels (as well as vitamin D deficiency) may be related to increased risk of prostate cancer.³⁵ Vitamin D intake increases both calcium and phosphorus absorption. Although the increased levels of calcium associated with enhanced vitamin D status may be an indicator of benefit for those at risk for bone loss, elevated blood levels of calcium may also be associated with increased risk of heart disease. Elevated serum calcium levels induced by hypervitaminosis D are responsible for many of its primary adverse effects.

Acute overdose is associated with increased urinary frequency, nausea, vomiting, loss of appetite, diarrhea, muscle weakness, dizziness, and calcification of heart, blood vessels, and lungs; symptoms reverse after overdosing is discontinued.

Adverse Effects Among Specific Populations

Individuals with sarcoidosis, other granulomatous diseases, and certain types of lymphoma may quickly develop elevated levels of 1,25(OH)₂-vitamin D₃ (the activated form), if supplemented with cholecalciferol or other vitamin D precursor, because of autonomous conversion of 25-OHD to the active hormone, 1,25(OH)₂D. Elevated levels of activated vitamin D significantly increase risk of hypercalcemia, which might require treatment with hydration, intravenous bisphosphonates, ketoconazole, hydroxychloroquine (Plaquenil), and corticosteroids, as well as avoidance of dietary sources of vitamins D₂ and D₃ and calcium.

Pregnancy and Nursing

Vitamin D enters breast milk and is considered compatible at usual dosage levels.

Infants and Children

Vitamin D intakes of 50 to 75 µg (2000-3000 IU) per day may cause toxicity symptoms in some children. Also, some

hypersensitive infants have developed toxicity symptoms at 1000 IU/day.

Most cases of toxicity involve the intake of 625 to 1500 µg (25,000-60,000 IU) per day for 1 to 4 months.

Children taking 250 µg (10,000 IU) per day for 4 months can develop the following toxicity symptoms, related to hypercalcemia: headaches, weakness, nausea and vomiting, constipation, polyuria, polydipsia, diarrhea, and calcification of soft tissues, such as kidneys, lungs, tympanic membrane, or ears.

Contraindications

Hypercalcemia, hyperparathyroidism (primary), hypersensitivity to cholecalciferol or any component of the formulation, malabsorption syndrome, sarcoidosis, granulomatous disease, lymphoma; evidence of vitamin D toxicity. If vitamin D insufficiency or deficiency is documented in a patient with lymphoma, cautious supplementation of vitamin D₃ with monitoring of blood levels of both forms of vitamin D and calcium may be undertaken. Not all lymphomas will autonomously convert 25-OHD to its activated form, and no predictive tests yet exist for this capability. Successful treatment of the lymphoma with a complete response obviates the risk of vitamin D hyperconversion. Vitamin D sufficiency may decrease risk of relapse in treated lymphoma patients because vitamin D deficiency is associated with increased risk of developing the disease (along with several other cancers, including breast, colon, and prostate).

Precautions and Warnings

Administer with extreme caution in patients with impaired renal function, heart disease, renal stones, or arteriosclerosis.

Administer concomitant calcium supplementation.

Maintain adequate fluid intake.

Avoid hypercalcemia, although not likely in absence of 1,25(OH)₂-vitamin D₃ excess.

Caution may be appropriate with renal function impairment with secondary hyperparathyroidism. However, impaired renal function is often associated with a need to administer prescription vitamin D as well as D₃ because second hydroxylation of the 25-OH form is lacking. Furthermore, secondary hyperparathyroidism is an indication for D₃ therapy.

INTERACTIONS REVIEW

Strategic Considerations

Several classes of common pharmacological agents interact with vitamin D and its metabolic processes. These interactions take on greater significance in light of the elevated probability of vitamin D deficiency in many of the patient populations likely to be prescribed the medications under consideration. More broadly, the occurrence of vitamin D deficiency has been recognized as being more widespread than previously believed, and in turn the implications of vitamin D insufficiency for health maintenance and disease prevention have become better understood. Thus, although conventional medical practice and governmental nutritional policies have focused on prevention of short-latency deficiency diseases, vitamin D represents a prime example of the growing awareness of the central role of nutritional factors in health maintenance and prevention of long-latency deficiency diseases. Factors such as lack of time outdoors with significant sunlight exposure, air pollution, cultural practices,

and geographic population distribution all add to the subtle but profound significance of seasonal decrease in sunlight availability, even in areas generally considered as “sunny.”^{7,9,11,36,37} The combined effect of these many factors contributes to what some experts have described as an “epidemic” of vitamin D deficiency, affecting 20% to 60% of the population.

The issues of pervasive vitamin D deficiency status and underutilization of laboratory assessment for 25-hydroxyvitamin D levels influence and limit research design, interpretation, and clinical practice within conventional medicine. For example, in 2005, two randomized controlled trials of calcium carbonate and cholecalciferol (vitamin D₃) administration for prevention of fractures in primary care reported widely publicized conclusions that such nutrient supplementation provided no value in preventing fractures.^{38,39} Such declarations were made despite disclosures that (1) vitamin D levels had been tested in only a small sample of the subjects in one of the studies; (2) vitamin D deficiency appeared to be common within the subject populations, as indicated by responses to vitamin D supplementation; (3) quality control of the supplements was very poor, and compliance was marginal and declined over time (e.g., 63%, or as low as 45%); and (4) the use of calcium carbonate in a population of older and often hypochlorhydric subjects would be considered suboptimal by many, if not most, experienced practitioners of nutritional therapeutics. Digestion of calcium carbonate relies on the integrity of gastric function and the bowel culture to produce the ionizing acids. Thus, gastrointestinal adverse effects, typical of calcium carbonate, were cited as a major factor in greater noncompliance with calcium intake.

In the study in which 1% of the subjects had their vitamin D levels actually measured, there was only a marginal increase after 1 year of supplementation with 800 IU of vitamin D per day (although some supplements, when analyzed, contained as little as 372 IU, mean value, per tablet). Average 25-OHD levels at beginning of the study (15 ng/mL) were in the range of severe deficiency and after 1 year improved only to 24 ng/mL, still well below what many vitamin D researchers consider to be adequate levels (30–40 ng/mL).⁴⁰

Subsequently, in a trial involving 944 healthy Icelandic adults, Steingrimsdottir et al.⁴¹ found that with 25-OHD levels below 10 ng/mL, maintaining calcium intake above 800 mg/day appeared to normalize calcium metabolism, as determined by the PTH level, but in individuals with higher 25-OHD levels, no benefit was observed from calcium intake above 800 mg/day. Likewise, Jackson et al.⁴² found that the combination of 1000 mg elemental calcium (as calcium carbonate) and 400 IU vitamin D daily did not appreciably reduce risk of hip fracture over 7 years, except in those who took their nutrients regularly. Thus, among adherent women (i.e., those who followed the treatment protocol 80% of the time), the supplements reduced hip fractures by 29%. Nevertheless, the relatively low dose of vitamin D, the use of calcium carbonate (a less-than-optimal form in the opinion of many and one associated with reduced compliance), and the late start and relatively limited duration of supplementation suggest that the treatment protocol was less than adequate (unless consistently adhered to) and thus render these findings less than conclusive. Such studies also indicate the importance of nutrient support throughout adulthood, as opposed to beginning it past midlife. Clearly, further research on calcium and other minerals involved in bone metabolism needs to take into account, and preferably optimize, vitamin D status.

Notably, the main conventional pharmacological intervention against osteoporosis is *antiresorptive drugs*, such as

bisphosphonates, for which almost every clinical trial has included coadministration of calcium or vitamin D. Moreover, the decontextualization and narrow focus of these studies highlight the shortcomings of standard research methodology and clinical practice to account for the broad factors of aging, lifestyle, activity level, drug depletions, and poor nutritional status characteristic of the populations in question, as well as the complex nature of bone health and its reliance on interdependencies of multiple nutrients and tissues, rather than such a narrow focus on supplemental calcium and vitamin D. As public and practitioner attention on vitamin D grows, it may prove a pivotal issue in expanding perceptions and awareness, analysis, and intervention through a broad integrative model more accurately reflecting patient needs and scientifically comprehending the breadth and complexity of the processes involved.^{14,24,28,37}

The well-known interactions between vitamin D and pharmaceutical medications cluster into several main groups. The use of calcium and vitamin D appears to enhance the bone-maintaining effectiveness of hormone replacement therapy (HRT) and bisphosphonates, especially for women who already have osteoporosis; this benefit appears greater for women supplementing with calcium citrate than for those using calcium carbonate. Anticonvulsants, particularly phenobarbital and phenytoin, may reduce serum levels of calcidiol (25-hydroxycholecalciferol, calcifediol) by altering hepatic metabolism of vitamin D. Notably, physicians prescribing agents that impair vitamin D function for extended periods (e.g., anticonvulsants, opioids, oral corticosteroids) usually do not advise or prescribe adequate countermeasures, whether vitamin D and calcium, bisphosphonates, or the combination, to effectively address the common occurrence of drug-induced decreases in bone mineral density and increased risk of fracture.^{43,44} Numerous medications that alter fat absorption, such as cholestyramine, colestipol, mineral oil, orlistat, and olestra, can interfere with intestinal absorption of vitamin D. Ketoconazole can reduce serum levels of calcitriol. Conversely, excessive vitamin D intake may, in rare cases, induce hypercalcemia and could theoretically precipitate cardiac arrhythmia in patients receiving cardiovascular medications such as verapamil or digoxin. Moreover, cardiac glycosides could potentially increase toxicity. Thiazide diuretics may increase vitamin D effects. Finally, it is now recognized that cholecalciferol inhibits CYP2C8/9, 2C19, and 2D6, although the full implications of such activity and the potential effects on pharmaceuticals metabolized by these enzymes have yet to be fully investigated and documented.

Because vitamin D toxicity from supplemental sources is a real (though improbable) possibility, health care providers are reminded to counsel their patients to avoid taking more than the recommended amount of vitamin D, and to take it in conjunction with a calcium supplement and possibly a special diet. The encouragement of greater exposure to sunlight (outdoors) cannot be overemphasized. Although contrary to prevailing dogma of the past decade and as yet poorly studied, it is becoming increasingly evident that use of high-potency sunscreens that block UVB may significantly contribute to vitamin D deficit. Oral supplementation can be used to compensate for lack of adequate UV exposure from sunlight. However, significantly higher amounts of supplementation may be necessary than previously believed and currently available in most vitamin preparations. Titrating intake to blood level of 25-OHD is the most reliable way to ensure adequate intake.

Although some innovative therapeutic strategies are emerging using vitamin D analogs, most examples of such approaches are considered separately in a brief review later.

NUTRIENT-DRUG INTERACTIONS

Allopurinol

Allopurinol (Lopurin, Zyloprim)

Interaction Type and Significance

⊕⊕ **Beneficial or Supportive Interaction, with Professional Management**

Probability:

2. Probable

Evidence Base:

○ **Preliminary**

Effect and Mechanism of Action

The uric acid-lowering agent allopurinol may elevate serum concentrations of 1,25-dihydroxycholecalciferol, the active form of vitamin D. Uric acid may directly decrease the serum concentration of 1,25(OH)₂-vitamin D₃ in patients with gout by inhibiting 1-hydroxylase activity.

Research

Takahashi et al.⁴⁵ measured the serum concentrations of 1,25(OH)₂-vitamin D₃, 25(OH)-vitamin D₃, and parathyroid hormone (PTH) in 82 male patients with primary gout whose serum uric acid was significantly higher than that of 41 normal control male subjects. The patients with gout exhibited a significantly decreased serum concentration of 1,25(OH)₂-vitamin D₃, which was corrected as uric acid levels dropped. These researchers reported that administration of allopurinol for 1 year caused a significant increase in their serum 1,25(OH)₂-vitamin D₃ concentration (along with a significant decrease in their serum uric acid concentration). Notably, the serum concentrations of 25(OH)-vitamin D₃ and PTH were not affected.

Nutritional Therapeutics, Clinical Concerns, and Adaptations

Individuals diagnosed with gout may have compromised vitamin D status and should be assessed for vitamin D deficiency. Coadministration of a uric acid-lowering agent such as allopurinol may elevate 1,25(OH)₂-vitamin D₃ levels. Supplementation with vitamin D (5-10 µg/day) may be advisable and is unlikely to present any significant risk, particularly under reasonable supervision and regular monitoring.

Androgen-Deprivation Therapy

Antiandrogens: Bicalutamide (Casodex), cyproterone (Androcur, Cyprostat, Cyproteron, Cyprone, Cyprohexal, Ciproterona, Cyproteronum, Neoproxil, Procur, Siterone), flutamide (Chimax, Drogenil, Euflex, Eulexin), nilutamide (Anandron, Nilandron).

Gonadotropin-releasing hormone (GnRH) agonists/analogs: Goserelin (Zoladex), leuprolide (Eligard, Lupron, Lupron Depot, Viadur), triptorelin (De-capeptyl Trelstar, Trelstar LA).

Interaction Type and Significance

☼ **Prevention and Reduction of Drug Adverse Effect**
⊕⊕ **Beneficial or Supportive Interaction, with Professional Management**

Probability:

2. Probable

Evidence Base:

● **Consensus**

Effect and Mechanism of Action

Decreased levels of sex hormones are generally associated with increased risk of diminished bone mineral density (BMD) and

osteoporosis. Supplementation of vitamin D can optimize and preserve bone mass, which tends to be adversely affected by androgen-deprivation therapy (ADT) and is associated with increased risk of osteoporosis and fractures.

Research

Research directly investigating prevention and treatment of osteoporosis caused by ADT is limited. Normally, the incidence of osteoporotic fractures usually increases a decade later in men than in women. Osteoporosis in men with gonadal steroid deficiency can derive from a variety of causes. Gonadotropin-releasing hormone agonists (which, after causing an initial surge in testosterone, result in castrate levels that are maintained as long as the drug is administered) hasten this process and increase bone loss, increasing the risk of osteoporosis and fractures, which have been widely documented in men prescribed ADT for the treatment of prostate carcinoma.⁴⁶⁻⁵³ Four retrospective studies have shown a significant association between ADT and elevated fracture risk in men with prostate cancer.^{48,54-56} In particular, with GnRH agonists, men with fractures had lower BMD and higher biochemical markers of bone resorption than men without fractures.⁵⁵ Collectively, the available studies indicate that the first year of ADT results in a 5% to 10% decrease in BMD in men with prostate cancer, an effect greater than that associated with menopause.⁵⁷ Furthermore, in a cross-sectional study of hormone-naïve men with prostate cancer, Smith et al.⁵⁸ observed vitamin D deficiency and inadequate dietary intake of calcium in 17% and 59%, respectively.

Smith et al.⁵⁹ also found that concurrent treatment with calcium, vitamin D, and pamidronate (a bisphosphonate drug) during ADT increases serum concentrations of both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. Bisphosphonates have come to play an important role in supporting bone mass.⁵⁹⁻⁶² Coadministration of vitamin D (and calcium), particularly with bisphosphonates, is generally accepted.⁵¹ The rationale and supporting research are further discussed in the Bisphosphonates section.

Nutritional Therapeutics, Clinical Concerns, and Adaptations

As with postmenopausal women and HRT, concomitant calcium and vitamin D enable and enhance the fundamental preventive support provided by diet and regular weight-bearing exercise in maintaining (or restoring) bone health, particularly bone mass and BMD. Smoking cessation, moderate alcohol consumption, and other supportive lifestyle modification should be also encouraged. The administration of bisphosphonates constitutes a further intervention as part of conventional care. Clinical management should evolve in response to the results of urinary assessment of bone breakdown (e.g., deoxypyridinium metabolites) and radiographic, DXA (dual-energy x-ray absorptiometry), ultrasound, or other techniques for BMD assessment. Oral intake of the bisphosphonate and calcium should be separated by at least 2 hours.

Anticonvulsant Medications, Including Phenobarbital, Phenytoin, and Valproic Acid

Evidence: Divalproex semisodium, divalproex sodium (Depakote), gabapentin (Neurontin), phenobarbital (phenobarbitone; Luminal, Solfoton), phenytoin (diphenylhydantoin; Dilantin, Phenytek), sodium valproate (Depacon), valproate semisodium, valproic acid (Depakene, Depakene Syrup).

Extrapolated, based on similar properties: Carbamazepine (Carbatrol, Tegretol), clonazepam (Klonopin), clorazepate (Tranxene), diazepam (Valium), ethosuximide (Zarontin),

ethotoin (Peganone), felbamate (Felbatol), fosphenytoin (Cerebyx, Mesantoin), lamotrigine (Lamictal), levetiracetam (Keppra), mephenytoin, mephobarbital (Mebaral), methsuximide (Celontin), oxcarbazepine (GP 47680, oxycarbamazepine; Trileptal), piracetam (Nootropyl), primidone (Mysoline), topiramate (Topamax), trimethadione (Tridione), vigabatrin (Sabril), zonisamide (Zonegran).

Interaction Type and Significance

≈≈≈ **Drug-Induced Nutrient Depletion, Supplementation Therapeutic, Not Requiring Professional Management**

◇ **Adverse Drug Effect on Nutritional Therapeutics, Strategic Concern**

☼ **Prevention or Reduction of Drug Adverse Effect**

Probability:

2. Probable

Evidence Base:

● **Consensus**

Effect and Mechanism of Action

Phenobarbital and related anticonvulsants are inducers of cytochrome P450 and the mixed-function oxidase system. Phenobarbital impairs bioavailability of vitamin D. Phenytoin and phenobarbital may reduce serum levels of 25(OH)D (calcidiol) by altering hepatic metabolism of vitamin D, at least in part by accelerating its metabolism.^{63, 64} Antiepileptic drugs (AEDs) that induce the enzyme CYP3A4 are of particular concern because 3A4 degrades vitamin D, which can create effects consistent with secondary hyperparathyroidism; AEDs that induce 3A4 include phenytoin, phenobarbital, carbamazepine, oxcarbazepine, and felbamate. Vitamin D therapy does not appear to alter serum phenytoin levels, but phenytoin may limit the ability of some individuals to respond to vitamin D therapy or may require larger doses of vitamin D to maintain optimal blood levels of 25-OHD. Thus, anticonvulsants impair mineralization, leading to increased risk of osteomalacia and osteoporosis.

High-dose vitamin D therapy can significantly counter vitamin D depletion and improve BMD and prevent bone loss associated with anticonvulsant treatment.

Research

Long-term therapy with phenytoin and other anticonvulsants can disturb vitamin D and calcium metabolism and result in osteomalacia. Both epilepsy and anticonvulsant medications are independent risk factors for low BMD, regardless of vitamin D levels. Long-term anticonvulsant treatment can cause excessive metabolism and deficiency of vitamin D and is believed to be associated with decreased BMD and bone loss.

In a 1982 study of 30 adult epileptic patients, Zerwekh et al.⁶⁵ reported decreased serum 24,25-dihydroxyvitamin D concentration during long-term anticonvulsant therapy (with phenytoin, phenobarbital, or carbamazepine), with phenobarbital-treated patients exhibiting a significant decrease in serum 25(OH)D. They noted that various anticonvulsant agents appear to exert different effects on vitamin D metabolism.

After finding no pattern of low serum levels of vitamin D (25[OH]D) or radiological evidence of osteomalacia or rickets in more than 400 individuals using anticonvulsants in Florida, Williams et al.⁶⁶ concluded that the climate provided adequate exposure to sunshine and thereby prevented the development of anticonvulsant-induced osteomalacia or rickets. "In contrast to reports from northern climates, we found minimal evidence of anticonvulsant-induced bone disease." Subsequently, in a controlled trial, Riancho et al.⁶⁷ studied 17 ambulatory epileptic children taking anticonvulsants for two seasons with high

and low levels of solar radiation and observed that although serum 25-OHD concentrations were normal among medicated subjects during the summer, their levels were significantly lower than those of controls during the winter months.

In initiating a prospective 3-year study, Hunt et al.⁶⁸ found that, of 144 children and young adults who required anticonvulsant therapy, 52 were found to have serum alkaline phosphatase (ALP) levels elevated more than two standard deviations (SDs) above normal, and half of these showed signs of rickets or osteomalacia. After slow and gradual but varying rates of response to calcitriol, all patients showed significant lowering of serum ALP levels by 30 months of follow-up. In a later controlled study, Jekovec-Vrhovsek et al.⁶⁹ determined that bone strength improved (specifically, BMD increased) in 13 institutionalized children under long-term anticonvulsant therapy who were supplemented for 9 months with 0.25 µg daily 1,25-dihydroxycholecalciferol vitamin D, the activated form of vitamin D, and 500 mg daily calcium.⁶⁹

Telci et al.⁷⁰ compared bone turnover in 52 epileptic patients receiving chronic anticonvulsant therapy with 39 healthy volunteers as matched controls and found that the resorption phase of bone turnover is affected during chronic anticonvulsant therapy. Total serum ALP levels (a marker of bone formation) were significantly increased in patients from both genders compared with those of controls. Among male epileptic patients, urinary deoxypyridinoline levels (a marker of bone resorption) were significantly increased and 25-OHD levels significantly reduced compared with controls.⁷⁰

Farhat et al.⁷¹ compared the effects of various AEDs on bone density in 71 adults and children over at least 6 months. More than half the adults and children/adolescents had low serum 25-OHD levels. Although this finding did not correlate with their BMD, AEDs were strongly associated with decreased BMD in the adults, particularly at skeletal sites enriched in cortical bone. Furthermore, lower BMD was more consistently associated with enzyme-inducing agents (e.g., phenytoin, phenobarbital, carbamazepine, primidone) than with medications that did not induce enzymes (e.g., valproic acid, lamotrigine, clonazepam, gabapentin, topiramate, ethosuximide). These researchers concluded: "Generalised seizures, duration of epilepsy, and polypharmacy were significant determinants of bone mineral density."⁷¹

Although it has been generally established that certain AEDs constituted a risk factor for osteoporosis and fractures in postmenopausal women, data regarding men have largely been lacking. In findings presented at the First North American Regional Epilepsy Congress, Jetter et al.⁷² found that "enzyme-inducing AEDs do significantly affect vitamin D, calcium, and parathyroid hormone levels." In this study, researchers focused on phenytoin, phenobarbital, carbamazepine, oxcarbazepine, and felbamate as enzyme 3A4-inducing AEDs. Because 3A4 degrades vitamin D, they set out to determine whether levels of 25-hydroxyvitamin D₃ (25-OH-D₃), PTH, or calcium differed between men taking 3A4 enzyme-inducing AEDs and those taking other types of AEDs. The researchers obtained 25-OH-D₃, intact PTH, and calcium levels in 210 male veterans, age 20 to 89 (average, 58), who had been treated with AEDs for an average of 20.3 years. On analysis, they found that the 126 patients treated with at least one enzyme-inducing AED for at least the past 6 months exhibited an average 25-OH-D₃ level of 19.2 ng/mL, compared with 23.8 ng/mL in those taking non-enzyme-inducing AEDs (*p* = .005). The patients taking enzyme-inducing AEDs had a blood calcium level of 8.83 mg/dL, whereas the 64 treated with only non-enzyme-inducing AEDs for that

period exhibited levels of 9.16 mg/dL ($p = .00009$). The intact PTH levels averaged 52.5 pg/mL for patients on enzyme-inducing AEDs and 38.2 pg/mL for patients on non-enzyme-inducing AEDs ($p = .0002$). The 20 patients treated with divalproex sodium were analyzed separately. The authors concluded that the “findings suggest that a secondary hyperparathyroidism is associated with the use of these drugs and that dietary supplementation of vitamin D may be necessary to prevent osteoporosis.” Furthermore, the investigators emphasized that neurologists need to monitor BMD in men treated with these medications, parallel to recommendations regarding female patients.⁷²

In 2001, Valmadrid et al.⁷³ published a survey of practice patterns of neurologists. They found that only 41% of pediatric and 28% of adult neurologists performed routine evaluation of patients taking AEDs for either bone or mineral disease. Further, among those physicians who detected bone disease through such diagnostic testing, 40% of pediatric and 37% of adult neurologists prescribed either calcium or vitamin D. However, only 9% of pediatric and 7% of adult neurologists prescribed prophylactic calcium or vitamin D for patients receiving AED therapy.

In two parallel, randomized, controlled trials involving 72 adults (18-54 years old) and 78 children and adolescents (10-18 years), Mikati, Fuleihan, et al.⁷⁴ investigated the effects of two doses of vitamin D given over 1 year on BMD in ambulatory patients on long-term AED therapy. Adult subjects received either “low-dose vitamin D” (400 IU/day) or “high-dose vitamin D” (4000 IU/day), and children and adolescents received 400 or 2000 IU/day. At baseline, 34% of the adults were in the deficient range of vitamin D levels, and 46% were in the insufficient range; the parallel levels for children were 18% and 44%, respectively. Likewise, using DXA, baseline BMD in adults was lower than that of age-matched and gender-matched controls versus either a Western or an ethnically identical population. After treatment, none of the adults and only a few of the children in the high-dose group still exhibited vitamin D deficiency, and relatively few had vitamin D insufficiency. Furthermore, the authors demonstrated that “significant increases in BMD at all skeletal sites compared to baseline” after 1 year in the high-dose, but not in the low-dose, vitamin D group. Nevertheless, BMD at 1 year remained below normal. Notably, baseline BMD was normal in children (compared with age- and gender-matched controls), and both treatment groups “showed significant and comparable increases” in BMD. The authors concluded that in “ambulatory adults on antiepileptic drugs, high-dose vitamin D therapy substantially increased bone mineral density at several skeletal sites,” and that “both doses resulted in comparable increases in bone mass” in children. These findings represent the first clinical trials demonstrating that high-dose vitamin D therapy significantly improves BMD in patients receiving AED therapy.⁷⁴

Report

Duus⁷⁵ reported a case of several severe fractures in a patient following epileptic seizures. The patient had epileptic osteomalacia and responded well to vitamin D treatment.

Nutritional Therapeutics, Clinical Concerns, and Adaptations

Many individuals with epilepsy, especially children, lead restricted lifestyles and are often institutionalized or under other forms of full-time care. Such individuals not only experience the effects of the pathophysiology on vitamin D metabolism, but also tend to have compromised nutritional status

and restricted time outdoors in the sun, especially during winter months. Thus, sunlight represents an effective and low-risk method of supporting vitamin D status. Oral supplementation can also be recommended. A moderate dose of 400 to 1500 IU/day of vitamin D could exert a protective function for individuals using phenobarbital or phenytoin who are concerned about potential drug-induced rickets, osteomalacia, or osteoporosis. Pretreatment and posttreatment monitoring of serum 25-OHD and 1,25-(OH)₂D levels would also identify individuals at risk of treatment-induced and nutritional/sunlight-related deficiencies of vitamin D. Available evidence indicates that such supplementation does not represent a significant risk of interfering with the therapeutic activity of standard anticonvulsant agents. However, as previously suggested, regular exposure to sunlight represents an effective and low-risk method of supporting vitamin D status by providing adequate stimulation of endogenous synthesis of necessary levels of vitamin D. Others have advocated a proactive approach toward the risks of bone loss while voicing caution that given the increased risk of osteomalacia, osteoporosis, and rickets among those taking anticonvulsants, withdrawal from such drugs carries potential for increased risk of seizure-related fractures. Monitoring of bone status is often appropriate.

Bisphosphonates

Evidence: Alendronate (Fosamax), etidronate (Didronel). Extrapolated, based on similar properties: Clodronate (Bonefos, Ostac), ibandronate (Bondronat, Boniva), risedronate (Actonel), tiludronate (Skelid), zoledronic acid (Zometa). Similar properties but evidence lacking for extrapolation: Pamidronate (Aredia).

Interaction Type and Significance

⊕⊕⊕ **Beneficial or Supportive Interaction, Not Requiring Professional Management**

Probability

2. Probable or
1. Certain

Evidence Base

⊙ Emerging or
● Consensus

Effect and Mechanism of Action

The ability of bisphosphonates to inhibit osteoclastic activity and bone resorption, maintain healthy bone mineralization, and produce substantial gains in bone mass depends on the presence of adequate vitamin D and other nutrients (e.g., protein, calcium, phosphorus).^{76,77} Calcium, the principal element in bone, can be absorbed in the brush border of the intestinal mucosa only when vitamin D is present. Notably, bisphosphonates have been used effectively to treat the more resistant cases of vitamin D-induced hypercalcemia.

Research

All currently approved, bone-active pharmacological agents have been studied only in conjunction with supplemental calcium, and newer anabolic agents increase mineral demand in skeletal tissue and will thus require even higher levels of calcium repletion.⁷⁸ The consensus underlying the fundamental importance of vitamin D and calcium nutrition is underscored by the observation that when Greenspan et al.⁷⁹ investigated the relative efficacy of HRT (conjugated estrogen with or without medroxyprogesterone) plus alendronate, HRT alone, alendronate alone, or placebo on spine and hip BMD in 373 osteopenic elderly women, all subjects received calcium and vitamin D supplements. After 3 years, DXA scans showed

that participants taking combination therapy had greater improvement in BMD at the hip and spine than those taking HRT or alendronate alone or taking placebo, all with calcium and vitamin D.

In an uncontrolled clinical trial involving osteoporosis patients with a poor response to bisphosphonate therapy, Heckman et al.⁸⁰ found that the addition of 25 µg (1000 IU) per day of vitamin D to the bisphosphonate regimen resulted in significantly increased BMD of the lumbar spine after 1 year. In a randomized, double-blind trial involving 48 osteopenic and osteoporotic women, Brazier et al.⁸¹ compared one group who received 10 mg alendronate once daily along with 500 mg elemental calcium daily and 10 µg (400 IU) cholecalciferol (vitamin D₃) twice daily for 3 months and a second group who received the same dosage of alendronate and calcium but placebo instead of the vitamin D. All subjects had low BMD, serum 25-hydroxyvitamin D₃ (25-OHD, calcifediol) less than 12 µg/L, and dietary calcium intake less than 1 g/day. Although markers of bone remodeling, such as serum and urinary CTX and urinary NTX (C- and N-terminal telopeptides of type I collagen), were dramatically and significantly decreased after as little as 15 days of treatment and remained decreased throughout the course of treatment in both groups, the group also receiving the vitamin D demonstrated a more pronounced effect, particularly after 1 month, for the bone resorption markers serum CTX and urinary NTX. These researchers concluded that coadministration of calcium and vitamin D is appropriate in elderly women with calcium and vitamin D insufficiencies receiving alendronate, to achieve rapid reduction of bone loss.⁸¹

In a randomized trial involving 154 patients with Crohn's disease, Siffledeen et al.⁸² investigated the efficacy of etidronate plus calcium and vitamin D for treatment of low BMD. The subjects, most of whom had T scores in the osteopenic range (−1.5 to −2.5), were administered etidronate (400 mg orally) or placebo for 14 days, and then both groups were given daily calcium (500 mg) and vitamin D (400 IU) for 76 days, in a treatment cycle repeated every 3 months for 2 years. After 24 months, BMD at the lumbar spine, ultradistal radius, and trochanter sites, but not the total hip, increased steadily, significantly, and similarly in both treatment arms. The findings demonstrate that in patients with low BMD on absorptiometry, treatment with calcium and vitamin D alone will increase BMD by about 4% per year, and that adding etidronate to the treatment program does not appear to enhance the effects of calcium and vitamin D.⁸² In an accompanying editorial on the preeminence of calcium and vitamin D in limiting fracture risk in Crohn's disease, Bernstein⁸³ commented that this study provides reassurance that bisphosphonates are "rarely needed in IBD [inflammatory bowel disease] patients, most of whom have T scores greater than −2.5, and many of whom are using corticosteroids to some extent."

Some patients with prostate carcinoma and a diffuse metastatic invasion of the skeleton exhibit indirect biochemical and histological indications of osteomalacia. Bisphosphonates are known to cause symptomatic hypocalcemia in prostate cancer patients with diffuse skeletal metastases. Bisphosphonate administration can aggravate osteomalacia and give the appearance of symptomatic hypocalcemia because of the transient, striking prevalence of osteoblastic activity over bone resorption by osteoclasts, which are inhibited by bisphosphonate drugs. Calcium supplementation is often considered as contraindicated in individuals with prostate cancer. However, concomitant use of calcium with bisphosphonates has been proposed as a means of inhibiting the osteoclastic activation that often

precedes the abnormal osteoblastic bone formation within metastases.

In regard to men with nonmetastatic prostate cancer, findings from a small, randomized, double-blind, controlled trial conducted by Nelson et al.⁸⁴ showed that treatment with alendronate, 70 mg weekly, plus daily calcium and vitamin D, reversed bone loss in 56 men receiving antiandrogen therapy. In contrast, the 56 subjects taking placebo, calcium, and vitamin D lost bone density during the same period. Notably, among these 112 men, with an average age of 71, only 9% had normal bone mass, whereas 52% had low bone mass and 39% developed osteoporosis after an average 2 years of ADT.

Nutritional Therapeutics, Clinical Concerns, and Adaptations

Calcium and vitamin D are essential for maintaining bone mass and density and imperative to the success of drug therapies for inducing bone augmentation.⁷⁷ Deficiencies of both nutrients are common in the patient populations at highest risk for osteoporosis. The importance of exercise and sound nutrition (including adequate protein, calcium, and phosphorus intake) as foundational cannot be overemphasized and is supported by growing evidence. Calcium has a clearly demonstrated effect of enhancing estrogen's effects on bone metabolism. Further, most research indicates that consistent exposure to sunlight (excluding winter in northern latitudes) provides a safe and effective, as well as otherwise beneficial, method of elevating vitamin D levels. Doses of 1500 mg calcium and 800 IU vitamin D daily provide prudent nutritional support for osteoporosis prevention and treatment, or more exactly, 30 to 40 mmol calcium with sufficient intake vitamin D daily to maintain serum 25(OH)D levels above 80 nmol/L (~30 µg/L).⁷⁸

Thus, a synergistic combination of oral calcium and vitamin D, within the context of an active lifestyle, constitutes the core proactive intervention within integrative therapeutics for all individuals at high risk for osteoporosis, or a foundational treatment for diagnosed bone loss. Notably, low serum vitamin D levels have been associated with the incidence of falls in older women,⁸⁵ and vitamin D has been found to be helpful in reducing the incidence of falls, a major factor in fracture risk, by improving muscle strength, walking distance, and functional ability.⁸⁶ Also, hormone supplementation or replacement regimens (conventional HRT, bio-identical estrogens/progesterone, herbal hormone precursors/modulators) should be considered if indicated in women.

In addition to these primary and secondary therapies, a bisphosphonate can provide a potent intervention in reversing bone loss and supporting healthy bone mass. Whereas oral calcium preparations need to be taken at least 2 hours before or after the bisphosphonate to avoid pharmacokinetic interference, such timing of oral vitamin D intake is unnecessary because no evidence has indicated potential pharmacological interference with bisphosphonates or other components of the treatment. It is generally recommended that alendronate or etidronate be taken with a full glass (6-8 ounces) of plain water on an empty stomach, avoiding the recumbent position for at least 30 minutes to prevent the potential for severe esophageal irritation associated with incomplete transfer of the tablet to the stomach.

Calcitriol and Vitamin D Analogs

Alfacalcidol, calcitriol, dihydrotachysterol.

See also later discussion for therapeutics involving vitamin D analogs and other agents.

Interaction Type and Significance

- XX** Minimal to Mild Adverse Interaction—Vigilance Necessary
- XXX** Potentially Harmful or Serious Adverse Interaction—Avoid
- ◇◇** Drug-Induced Effect on Nutrient Function, Supplementation Contraindicated, Professional Management Appropriate

Probability:

1. Certain

Evidence Base:

● Consensus

Effect and Mechanism of Action

The simultaneous use of supplemental vitamin D and vitamin D analogs, such as calcitriol, inherently produces an additive effect. The potential for vitamin D toxicity is particularly increased because calcitriol [1,25(OH)₂D₃] and its drug formulations bypass physiological feedback mechanisms and control systems that normally limit its production in the kidneys. The clinical significance and severity of the interaction primarily depend on the respective dosages involved and duration of intake, although individual variability based on VDR genotype, diet, and other factors may modify the intensity and character of the response.

Research

Research into coordinated administration of supplemental vitamin D and vitamin D analogs represents a viable approach to integrative therapeutics that has yet to be conducted in a systemic manner.

The use of calcitriol and other vitamin D analogs in combination with other pharmaceutical agents represents an emerging area of therapeutic synergy. Even though these agents are drugs and not nutrients per se, their action is derived from their relationship to vitamin D, and their therapeutic application is discussed briefly later.

Reports

Reports of vitamin D toxicity resulting from simultaneous intake of vitamin D and pharmaceutical analogs are lacking.

Clinical Implications and Adaptations

Coadministration of vitamin D and analogs such as calcitriol may be appropriate in some circumstances, as in renal disease, but only under close medical supervision. Unintentional concomitant use of vitamin D and its pharmacological analogs should be avoided through direct inquiry by health care providers of patients initiating therapy and routine implementation of a thorough inventory of vitamin and other supplement intake.

Cholestyramine, Colestipol, and Related Bile Acid Sequestrants

Evidence: Cholestyramine (Locholest, Prevalite, Questran), colestipol (Colestid).

Extrapolated, based on similar properties: Colesevelam (WelChol).

Interaction Type and Significance

- ≈≈≈** Drug-Induced Nutrient Depletion, Supplementation Therapeutic, Not Requiring Professional Management
- ◇** Adverse Drug Effect on Nutritional Therapeutics, Strategic Concern

Probability:

4. Plausible

Evidence Base:

○ Preliminary

Effect and Mechanism of Action

Absorption of dietary sources of vitamin D requires bile. Bile acid sequestrants, such as cholestyramine and colestipol, decrease lipid digestion and absorption. In the process, they also reduce absorption of the fat-soluble vitamins, such as vitamin D, and other nutrients.⁸⁷⁻⁸⁹

Research

Tonstad et al.⁹⁰ conducted a study of 37 boys and 29 girls age 10 to 16 years with familial hypercholesterolemia, first in an 8-week, double-blind, placebo-controlled protocol, then in open treatment for 44 to 52 weeks. After 1 year of colestipol, those who took 80% or more of the prescribed dose had a greater decrease in serum 25-OHD levels than those who took less than 80%. They also found that levels of serum folate, vitamin E, and carotenoids were reduced in the colestipol group.⁹⁰

In a rodent model, Watkins et al.⁹¹ found that cholestyramine may deplete calcium (and zinc), an effect that could adversely impact the function of vitamin D, especially in regard to bone health.

Nutritional Therapeutics, Clinical Concerns, and Adaptations

Fat-soluble vitamins, and vitamin D nutriture in particular, can play a valuable role in the prevention and treatment of many conditions involving the cardiovascular system and lipid metabolism (including atherosclerosis, heart disease, obesity, hypertension, and diabetes), such that interference with its absorption could be counterproductive in relation to the broad therapeutic strategy and clinical outcomes. Modest supplementation with vitamin D (10-20 µg or 400-800 IU daily) may be advisable for many individuals, particularly those at high risk for deficiency sequelae, but consistent exposure to sunlight (without sunscreen) may be sufficient to maintain healthy vitamin D levels and can be combined with the exercise usually critical to those prescribed bile acid sequestrants. Exposure to sunlight in the winter months of higher latitudes, however, is likely to be insufficient to maintain adequate vitamin D levels, making dietary use of supplements or a rich natural source of vitamin D (e.g., cod liver oil) necessary, separated from the bile acid sequesterant by at least 2 hours.

Cimetidine

Cimetidine (Tagamet)

Interaction Type and Significance

- ≈≈≈** Drug-Induced Nutrient Depletion, Supplementation Therapeutic, Not Requiring Professional Management
- ◇** Adverse Drug Effect on Nutritional Therapeutics, Strategic Concern

Probability:

4. Plausible

Evidence Base:

○ Preliminary

Effect and Mechanism of Action

Cimetidine inhibits vitamin D hydroxylase (a hepatic mixed-function oxidase) and may reduce hepatic activation of vitamin D through hydroxylation.⁹²

Research

In limited animal and human research, cimetidine has been found to decrease the synthesis of vitamin D and adversely affect serum levels of 25-OHD.

In a small, uncontrolled trial, Odes et al.⁹³ treated nine adult subjects with 400 mg cimetidine orally twice daily

during a period from winter to summer, as the daily duration of sunlight was increasing. They measured serum levels of 25-OHD, 24,25(OH)₂D, and 1,25(OH)₂D before treatment, after 4 weeks of treatment, and 1 month after cessation of treatment. The normal seasonal increase in the level of 25-OHD was not observed during treatment. However, 25-OHD did rise significantly after the cimetidine was withdrawn. These researchers concluded that their findings “suggest that short-term treatment with cimetidine could potentially perturb vitamin D metabolism in man.”

Further clinical trials would be necessary confirm these preliminary findings and to determine whether other H₂ receptor antagonists might similarly affect vitamin D metabolism in humans.

Nutritional Therapeutics, Clinical Concerns, and Adaptations

Laboratory tests can determine blood levels of 25-hydroxycholecalciferol, the form of vitamin D after it has been hydroxylated in the liver. Low levels require prescription of an activated form of vitamin D (e.g., calcitriol) because activation of a regular vitamin D supplement (or even cholecalciferol derived from sunlight exposure) would be vulnerable to blockage by the cimetidine. In this case it would be prudent to monitor the serum level of 1,25-dihydroxyvitamin D to be certain that replacement is adequate but not excessive.

Corticosteroids, Oral, Including Prednisone

Betamethasone (Celestone), cortisone (Cortone), dexamethasone (Decadron), fludrocortisone (Florinef), hydrocortisone (Cortef), methylprednisolone (Medrol) prednisolone (Delta-Cortef, Orapred, Prediapred, Prelone), prednisone (Deltasone, Liquid Pred, Meticorten, Orasone), triamcinolone (Aristocort).

Similar properties but evidence indicating no or reduced interaction effects: Inhaled or topical corticosteroids.

Interaction Type and Significance

- ≈≈≈ Drug-Induced Nutrient Depletion, Supplemental Therapeutic, Not Requiring Professional Management
- ◇≈≈ Drug-Induced Adverse Effect on Nutrient Function, Coadministration Therapeutic, with Professional Management
- ◇ Adverse Drug Effect on Nutritional Therapeutics, Strategic Concern

Probability:

2. Probable, 3. Possible

Evidence Base:

○ Emerging

Effect and Mechanism of Action

Oral corticosteroids are associated with osteoporosis. The mechanism is multifactorial, including reduced calcium absorption, decreased vitamin D availability, lowered serum 25-hydroxycholecalciferol levels, and interference with vitamin D activation and metabolism, all increasing risk of bone loss.⁹⁴⁻⁹⁹ Corticosteroids also contribute to osteoporosis through increased renal calcium excretion and decreased bone formation by osteoblasts and serum levels of sex hormones. Administration of cortisone impairs net calcium absorption through two mechanisms: depressed vitamin D–dependent calcium absorption and increased vitamin D–independent calcium backflux.¹⁰⁰

Research

It is generally recognized that long-term use of corticosteroids can lead to loss of bone mineral density (BMD) and higher risk

for fractures. Of patients using corticosteroids for long periods, 25% develop at least one fracture. Although the usefulness of calcium and vitamin D supplements in the treatment and the prevention of steroid-induced osteoporosis may seem self-evident, research into the effectiveness of such nutritional therapies has been slow to evolve. Nevertheless, it now appears that the adverse effects of glucocorticosteroids on intestinal calcium transport and bone turnover can usually be counteracted by the combined administration of supplemental doses of calcium and physiological doses of 25-OHD₃.

In 1977, Hahn et al.¹⁰¹ observed no significant serum 25-OHD concentrations in 21 adults receiving chronic, moderate-dose corticosteroid therapy and who demonstrated radiological osteopenia (vs. controls). However, in 1978, Chesney et al.⁹⁸ found a reduction of serum 1,25(OH)₂D in children receiving long-term glucocorticoid treatment for various glomerular diseases (vs. children with chronic glomerulonephritis but not treated with glucocorticoids). They further observed that this reduction in serum 1,25(OH)₂D₃ concentration correlated with the dose of steroid administered as well as with the severity of reduction in forearm bone mineral content.

By administering 20 mg/day of prednisone to 12 normal adults for 14 days, Hahn et al.⁹⁴ confirmed that glucocorticoids suppress intestinal calcium absorption (by 31%), but not by decreasing circulating concentrations of biologically active vitamin D metabolites, since mean serum concentrations of 25-OHD and 24,25(OH)₂D did not change significantly from initial values; serum 1,25(OH)₂D concentration was even slightly increased.

In a 2-year, randomized, double-blind, placebo-controlled trial, Buckley et al.¹⁰² administered 500 IU of vitamin D₃ and 1000 mg of calcium carbonate daily to 65 rheumatoid arthritis patients being treated with low amounts of prednisone (mean dosage, 5.6 mg daily). They found that those who received the nutrients maintained or gained BMD in the lumbar spine and trochanter, whereas those receiving prednisone therapy but were given placebo (i.e., no supplements) lost BMD in the same areas during the course of the study. In a subsequent study (1998), Lems et al.¹⁰³ reported that low-dose (10 mg/day) prednisone (LDP) treatment led to a decrease in osteocalcin, P1CP, and alkaline phosphatase and an increase in urinary excretion of calcium. They concluded that LDP has a negative effect on bone metabolism because bone formation decreased while bone resorption remained unchanged or decreased slightly. They also found parathyroid hormone (PTH) increased (insignificantly) during LDP (+19%) and LDP plus calcium (+14%), but decreased during coadministration of with calcitriol (–16%) and calcium/calcitriol (–44%). The increase in PTH during LDP could be prevented by calcitriol combined with calcium supplementation.

Wissing et al.¹⁰⁴ conducted a 1-year controlled trial investigating the effect of low-dose corticosteroids on post-renal transplant bone loss and the ability of cholecalciferol to further decrease bone loss. They administered either 400 mg oral calcium or 400 mg oral calcium daily in association with a monthly dose of 25,000 IU vitamin D₃ to 90 patients admitted for renal transplantation and scheduled to be treated with low doses of prednisolone. All subjects experienced a “moderate but significant” loss of lumbar spine BMD, but no bone loss at the femoral neck and shaft during the first posttransplant year. Subjects in the calcium/D₃ group had significantly higher 25-OHD but not 1,25(OH)₂D levels and exhibited slightly higher bone loss, but the difference did not reach statistical significance. The researchers also reported “a highly significant negative correlation between 25(OH) vitamin D and intact parathyroid

hormone (iPTH) serum levels.” They concluded that “cholecalciferol supplementation did not prevent posttransplant bone loss but contributed to the normalization of iPTH levels after renal transplantation.”¹⁰⁴ Notably, the dose administered, 25,000 IU of D₃ once a month, is less than the 1000 IU per day recommended by experts as the minimum for those not exposed to adequate sunlight, and it is not well timed for an agent with a half-life of 2 weeks.

A meta-analysis of well-designed clinical trials by Amin et al.¹⁰⁵ concluded that supplementation with vitamin D and calcium was more effective than placebo or calcium alone in providing a “moderate” protective effect against corticosteroid-induced osteoporosis, using change in lumbar spine BMD as the primary outcome measure. However, bisphosphonates and fluoride were more effective than vitamin D in some trials.

In contrast, numerous studies and several reviews of inhaled and nasal corticosteroids have consistently concluded that such medications, in and of themselves, do not generally pose a significant risk of inducing bone loss in children or adults.¹⁰⁶ For example, Elmstahl et al.¹⁰⁷ reported no difference in BMD in a group of subjects taking inhaled corticosteroids and unexposed control subjects, nor was any dose-response relationship observed between inhaled steroid therapy and BMD. Likewise, Suissa et al.¹⁰⁸ conducted a case-control study nested within a population-based cohort of all Quebec patients at least 65 years of age who were given respiratory medications and followed for at least 4 years. The rate of fracture for current inhaled corticosteroid use was not increased, and the rate of upper extremity fracture increased by 12% (RR 1.12) with every 1000- μ g increase in the daily dose of inhaled corticosteroids. No such increase was observed for hip fracture. Among a subgroup of subjects followed more than 8 years, “only the use of more than 2000 μ g of inhaled corticosteroids per day for an average of 6 years was associated with an elevated risk of fracture.” No increase in the rate of fractures was observed at any dose of nasal corticosteroids.

Nutritional Therapeutics, Clinical Concerns, and Adaptations

Physicians prescribing corticosteroids, possibly for only 1 month but especially for longer periods, are advised to discuss the potential adverse metabolic implications of such medications with patients and compensatory options. In 1998, Lems et al.¹⁰⁹ noted that “in spite of guidelines according to which patients protractedly using corticosteroids should take sufficient calcium and cholecalciferol, only about one-tenth of them takes any form of medication to prevent osteoporosis.” Most research indicates that calcium intakes from dietary and supplemental sources totaling 1000 to 1500 mg of calcium per day in conjunction with 10 to 20 μ g (400-800 IU) of vitamin D are required to prevent adverse effects, although much higher doses may be necessary in the context of a preexisting 25OHD deficiency.⁴⁰ Monitoring serum levels of both 25-OHD and 1,25(OH)₂D (activated form of vitamin D) is appropriate, and supplementation (or possibly a prescription of calcitriol) is often necessary if a deficiency is indicated. If 25-OHD levels are low (<50 nmol/L), correction with up to 7000 IU vitamin D₃ per day, or 50,000 IU vitamin D₂ per week, for 1 to 2 months will correct the 1,25(OH)₂D level in patients with normal renal function. Often the 1,25(OH)₂D (dihydroxycholecalciferol) level is maintained, even in the face of a 25-OHD deficiency, due to increased secretion of PTH, which speeds up renal conversion of 25-OHD to the active form. Thus, measuring intact PTH, as well as both forms of vitamin D, provides the most complete picture of vitamin D status.⁴⁰ It is also prudent to monitor for

hypercalciuria and hypercalcemia when supplementing with both calcium and vitamin D, although the occurrence of hypercalcemia is rare.

Physicians prescribing steroids for longer than 2 weeks should encourage all patients to modify their lifestyles, including smoking cessation and limitation of alcohol consumption. The importance of mild to moderate weight-bearing exercise cannot be overemphasized; 30 minutes to 1 hour every day, particularly with sunlight exposure, should be strongly encouraged, if feasible. However, individuals with known or potential bone loss should be advised to develop an exercise program under the supervision of a physician or other health care professional familiar with the increased risks of fracture associated with long-term use of steroids.

Some physicians may consider it necessary and appropriate to prescribe calcitriol in individual cases. Concomitant use of bisphosphonates and estrogen/progesterone support may also be appropriate for some individuals using oral steroids longer than 3 months, especially if low BMD is evident or likely.

Hormone Replacement Therapy (HRT): Estrogen-Containing and Synthetic Estrogen and Progesterone Analog Medications

Evidence: HRT, estrogens: Chlorotrianisene (Tace); conjugated equine estrogens (Premarin); conjugated synthetic estrogens (Cenestin); dienestrol (Ortho Dienestrol); esterified estrogens (Estratab, Menest, Neo-Estrone); estradiol, topical/transdermal/ring (Alora Transdermal, Climara Transdermal, Estrace, Estradot, Estring FemPatch, Vivelle-Dot, Vivelle Transdermal); cestradiol cypionate (Dep-Gynogen, Depo-Estradiol, Depogen, Dura-Estrin, Estra-D, Estro-Cyp, Estroject-LA, Estronol-LA); estradiol hemihydrate (Estreva, Vagifem); estradiol valerate (Delestrogen, Estra-L 40, Gynogen L.A. 20, Progynova, Valergen 20); estrone (Aquest, Estragyn 5, Estro-A, Estrone ‘5’, Kestrone-5); estropipate (Ogen, Ortho-Est); ethinyl estradiol (Estinyl, Gynodiol, Lynoral).

HRT, estrogen/progestin combinations: Conjugated equine estrogens and medroxyprogesterone (Premelle cycle 5, Prempro); conjugated equine estrogens and norgestrel (Prempak-C); estradiol and dydrogesterone (Femoston); estradiol and norethindrone, patch (CombiPatch); estradiol and norethindrone/norethisterone, oral (Activella, Climagest, Climesse, FemHRT, Trisequens); estradiol valerate and cyproterone acetate (Climens); estradiol valerate and norgestrel (Progyluton); estradiol and norgestimate (Ortho-Prefest). Related but evidence lacking for extrapolation: HRT, estrogen/testosterone combinations: Esterified estrogens and methyltestosterone (Estratest, Estratest HS).

HRT, progestins: Dydrogesterone (Duphaston), intrauterine L-norgestrel system (Mirena), medroxyprogesterone acetate (Provera), norethisterone (norethindrone; Micronor).

HRT, progesterone: Micronized progesterone (Prometrium, Utrogestan).

Medroxyprogesterone: Conjugated equine estrogens and medroxyprogesterone (Premelle cycle 5, Prempro); medroxyprogesterone, oral (Cycrin, Provera); medroxyprogesterone, injection (depot medroxyprogesterone acetate, DMPA; Depo-Provera, Depo-subQ Provera 104); progestin and estrogen injectable: estradiol cypionate and medroxyprogesterone acetate (Cyclofem, Lunelle).

Interaction Type and Significance

⊕⊕ **Beneficial or Supportive Interaction, with Professional Management**

×× **Minimal to Mild Adverse Interaction—Vigilance Necessary**

Probability:

3. Possible or
2. Probable

Evidence Base:

○ Emerging

Effect and Mechanism of Action

The combination of vitamin D and estrogen replacement therapy (ERT, in the context of calcium supplementation) increases bone mass more than ERT alone, especially in osteoporotic women. The ability of exogenous female hormones, particularly forms of estrogen, to effectively inhibit osteoclastic activity and bone resorption, maintain healthy bone mineralization, and support bone mass is inherently dependent on the presence of vitamin D and other nutrients (e.g., protein, calcium, phosphorus).^{76,77} Calcium, the principal element in bone, can be absorbed in the brush border of the intestinal mucosa only when vitamin D is present. Estrogen appears to have a beneficial effect on vitamin D (and calcium) metabolism, although progestins may diminish that benefit. Estrogen also inhibits osteoclastic action, which would represent an additive interaction with vitamin D.

Research

The negative calcium balance usually associated with aging is accentuated in osteoporotic women who have decreased calcium absorption and decreased serum levels of $1,25(\text{OH})_2\text{D}$. In a controlled trial involving 17 women with surgically induced menopause, Lobo et al.¹¹⁰ (1985) observed that serum levels of $1,25(\text{OH})_2\text{D}$ increased and urinary calcium loss decreased after 2 months of conjugated estrogens (0.625 mg daily).¹¹⁰ Subsequently, several studies have investigated various aspects of the question of whether such elevated vitamin D levels might correspond with increased bone strength and reduced risk of fractures and how this effect might vary given initial BMD status, for different individuals, under different HRT regimens, or with different forms of calcium.

Several studies have examined the role of HRT in improving vitamin D activity and calcium balance in women with postmenopausal osteoporosis. In an early study of postmenopausal women by Bikle et al.,¹¹¹ treatment with 17β -estradiol alone increased serum $1,25(\text{OH})_2\text{D}$, but the addition of medroxyprogesterone, a progestin, lowered vitamin D levels such that total and free $1,25(\text{OH})_2\text{D}$ returned toward baseline and thus appeared to antagonize part of the beneficial effects on calcium homeostasis attributable to estrogen. In the first prospective trial confirming the beneficial effect of HRT on prevention of peripheral fractures in nonosteoporotic postmenopausal women and subsequent controlled studies, Komulainen et al.¹¹²⁻¹¹⁴ determined that supplementation with 300 IU/day of vitamin D_3 (cholecalciferol) does not prevent bone loss in healthy, nonosteoporotic, early-postmenopausal women, nor does such low-dose vitamin D_3 provide significant benefit beyond that attributable solely to combined estradiol and progestin. However, in a 4-year, prospective, partly randomized study of 60 osteoporotic women, Tuppurainen et al.¹¹⁵ found that vitamin D_3 (cholecalciferol, 300 IU/day, no intake during June–August) together with a combination of 2 mg estradiol valerate and 1 mg of a progestin (cyproterone acetate) daily resulted in greater improvement in BMD compared with estradiol/progestin alone (as well as with baseline or placebo). The osteoporotic women in both HRT groups demonstrated a significant increase in lumbar BMD, but there were no statistically significant differences in either lumbar or femoral BMD changes between these two HRT groups. Furthermore, the combination of HRT and vitamin D_3 was associated with a greater increase in femoral neck BMD than with HRT alone.

In a randomized, double-blind, placebo-controlled trial involving 128 healthy Caucasian women over age 65 with low spinal BMD, Recker et al.¹¹⁶ compared parameters of BMD and bone loss under continuous low-dose HRT (conjugated equine estrogen, 0.3 mg/day, and medroxyprogesterone, 2.5 mg/day) in conjunction with calcium and vitamin D supplementation versus placebo. Subjects in both groups were administered sufficient calcium supplementation to bring all calcium intakes above 1000 mg/day and oral 25-OHD sufficient to maintain serum 25-OHD levels of at least 75 nmol/L. Through the course of 3.5 years of observation, significant increases were seen in spinal BMD as well as in total-body and forearm bone density, particularly among patients with greater than 90% adherence to therapy. Meanwhile, breast tenderness, spotting, pelvic discomfort, mood changes, and other symptoms typically associated with HRT were mild and short-lived under this relatively low-dose regimen. These authors concluded that “continuous low-dose HRT with conjugated equine estrogen and oral medroxyprogesterone combined with adequate calcium and vitamin D provides a bone-sparing effect that is similar or superior to that provided by other, higher-dose HRT regimens in elderly women” and is well tolerated by most patients.¹¹⁶

In a 6-month, placebo-controlled clinical trial involving 21 postmenopausal women with osteoporosis, Gallagher et al.¹¹⁷ observed that conjugated equine estrogen increased both calcium absorption and serum vitamin D levels [$1,25(\text{OH})_2\text{D}$]. Subsequently, these researchers investigated the roles of estrogen deficiency and declining calcium absorption from reduced activated vitamin D (calcitriol) levels or intestinal resistance to calcitriol as central factors in age-related bone loss. In a randomized, double-blind, placebo-controlled trial involving 485 elderly women (66–77 years old) with normal BMD for their age, Gallagher et al.¹¹⁸ compared the effects of ERT (0.625 mg conjugated estrogens daily for women without a uterus) and HRT (ERT plus 2.5 mg medroxyprogesterone acetate daily for those women with a uterus) with or without calcitriol ($1,25\text{-OHD}$) versus placebo. Hormone therapy alone and in combination with calcitriol were both highly effective in reducing bone resorption and increasing BMD at the hip and other key sites. In particular, calcitriol was effective in increasing BMD in the femoral neck and spine. The combination of ERT/HRT and calcitriol increased BMD in the total hip and trochanter significantly more than did ERT or HRT alone, particularly in women adherent to treatment. Thus, the concomitant use of vitamin D, calcium, and conventional forms of HRT appear generally to raise vitamin D levels but especially to enhance BMD in women who demonstrate osteoporosis, that is, those for whom BMD is most critical. Furthermore, such nutritional support may also allow for reduced HRT dosages and corresponding decrease in risk of attendant adverse effects and sequelae.

The form of calcium used for supplementation presents a potential confounding factor that has not been considered by most researchers but that would be a central concern to most practitioners of nutritional therapeutics. By examining data from a trial involving 25 postmenopausal women, Heller et al.¹¹⁹ (2002) found that variable results of reported calcium supplementation studies may be caused by the effects of estrogen treatment or vitamin D status on the bioavailability of calcium citrate versus calcium carbonate. Using data derived from a prior trial in 25 postmenopausal women, the authors found that change in area under the curve (ΔAUC) of serum calcium after subtraction of placebo was significantly higher

after calcium citrate than after calcium carbonate in non-estrogen-treated patients. Estrogen-treated patients showed no evident difference in the bioavailability of calcium between the two calcium formulations. Bioavailability was also significantly higher with the citrate salt for the subgroups with lower serum 25-OHD and higher serum 1,25(OH)₂D concentrations. Thus, bioavailability of calcium from calcium carbonate was more dependent on estrogen treatment and vitamin D status than that of calcium citrate.

Preliminary research into polymorphisms of the estrogen receptor (ER), vitamin D receptor (VDR), and their interactions may help clarify individual genetic variations in the influence of hormone therapies, exercise, ethnic background, and other factors on bone mineral density (BMD) and peak bone mass. In a population-based, 3-year, longitudinal study of BMD, Willing et al.¹²⁰ found that two genetic ER polymorphisms were significantly predictive of both lumbar spine and total-body BMD level, but not change in BMD during the study. A genetic VDR variant was not associated with baseline BMD, change in BMD over time, or any of the bone-related serum and body composition measurements in the 372 women in whom it was evaluated. Further, no other polymorphic markers were identified as being significantly associated with BMD measurements. However, these researchers did identify a significant impact on BMD levels associated with an interaction of two ER polymorphisms and two VDR genotypes. Subjects who had the (−/−) PvuII ER and bb VDR genotype combination had a very high average BMD, whereas women with the (−/−) PvuII ER and BB VDR genotype had significantly lower BMD levels. Differences in serum levels of osteocalcin, PTH, 1,25(OH)₂D, or 25(OH)₂D did not explain this contrast. These authors concluded that their findings “suggest that genetic variation at the ER locus, singly and in relation to the vitamin D receptor gene, influences attainment and maintenance of peak bone mass in younger women, which in turn may render some individuals more susceptible to osteoporosis than others.”¹²⁰

Subsequently, in a study involving 108 postmenopausal Caucasian women, Deng et al.¹²¹ found that VDR and ER genotypes may have different effects on BMD at different sites and on total-body bone mineral content (tbBMC). They assessed associations of BMD with VDR BsmI genotypes and ER XbaI (ERX) and PvuII (ERP) polymorphisms with spine, femoral neck, and distal radius BMD and with tbBMC. In this sample, researchers did not detect a significant association for ER genotypes with spine and radius BMD, or for VDR genotypes with femoral neck and radius BMD and tbBMC, or find a significant interaction between VDR and ER genotypes. However, they did note significant associations between (1) VDR genotypes and spine BMD variation, (2) both ERX and ERP genotypes and femoral neck BMD variation, and (3) ERX genotypes and tbBMC variation. Based on these observations, these researchers concluded that “if significant factors influencing bone are not appropriately controlled, true significant associations can easily be missed.”¹²¹ Related research suggests that bone may be more responsive to exercise in some genotypes of VDR than in others,¹ and that gene-environment interactions such as leisure physical activity and VDR genotype may play a role in maintaining the BMD at the lumbar spine in active postmenopausal women, especially older women.²

The importance of individual genotypes as important factors in determining changes in bone mass in the elderly, with and without HRT, as well as other factors, such as vitamin D and mineral nutrition and exercise, is becoming increasingly clear and will undoubtedly receive greater consideration in

shaping individualized therapeutic strategies to optimize and preserve bone mass.

Myrup et al.¹²² cautioned against a possible limiting effect of cholecalciferol on the lipid benefits of HRT, along with potential risk of hypercalcemia. In a double-blind, randomized trial involving 74 postmenopausal women, they investigated the effect of cholecalciferol and estrogen-norethindrone treatment for 1 year on total cholesterol level, high-density lipoprotein (HDL) cholesterol level, blood pressure, and body mass index. A similar decrease in serum cholesterol level was demonstrated in subjects receiving estrogen-norethindrone (11%) and those receiving hormones combined with cholecalciferol (13%); this hypocholesterolemic effect was most pronounced in lean women. However, the HDL cholesterol/total cholesterol ratio increased only 25% in women administered both estrogen-norethindrone and cholecalciferol, versus an increase of 45% with estrogen-norethindrone treatment alone.¹²² Subsequently, in a population-based, prospective, 3-year study involving 464 women, Heikkinen et al.¹²³ arrived at similar conclusions. They found that serum concentrations of HDL cholesterol did not change significantly in the group receiving HRT (sequential combination of 2 mg estradiol valerate and 1 mg cyproterone acetate) alone, but decreased in the groups receiving vitamin D₃, HRT plus vitamin D₃, or placebo.

Nutritional Therapeutics, Clinical Concerns, and Adaptations

Hormone support, calcium, and vitamin D act in concert to enhance the primary activities of nutrition and exercise in healthy bone metabolism. HRT has been the mainstay of osteoporosis prevention but is limited because of dose-related risks, adverse effects, and patient acceptance. Furthermore, because estrogen alone can be safely used only in women without a uterus, due to an unacceptably high incidence of uterine cancer with unopposed estrogen, all postmenopausal women with an intact uterus receiving hormonal therapy must be treated with some combination of estrogen and progestins or their analogs, even though estrogen's effect on bone appears potentiated by calcium and vitamin D, and progestins may work against it. Calcium and vitamin D are essential for maintaining bone mass and density and imperative to the success of drug therapies for inducing bone augmentation.⁷⁷ Deficiencies of both nutrients are common in the patient populations at highest risk for osteoporosis. The importance of exercise and sound nutrition (including adequate protein and phosphorus intake) as foundational cannot be overemphasized and is supported by growing evidence.^{2,124,125}

Calcium and estrogen have a clearly demonstrated synergistic effect of enhancing each other's effects on bone metabolism. Further, most research indicates that consistent exposure to sunlight provides a safe and effective, as well as otherwise beneficial, method of elevating vitamin D levels. Nevertheless, prudent nutritional support for osteoporosis prevention and treatment can be provided through diet or supplementation including 1500 mg/day of calcium and 800 IU (20 µg) vitamin D, or more exactly, sufficient intake vitamin D per day to maintain serum 25(OH)D levels above 80 nmol/L.⁷⁸

Thus, a synergistic combination of oral calcium and vitamin D, within the context of an active lifestyle, constitutes the core proactive intervention within integrative therapeutics for all individuals at high risk for osteoporosis, or a base treatment for diagnosed bone loss. Additionally, hormone supplementation or replacement regimens (conventional HRT, bio-identical estrogens/progesterone, isoflavones, herbal

hormone precursors/modulators) may produce the same effects, but conclusive evidence is lacking. Further research through well-designed clinical trials is warranted.

Although exogenous hormone therapy (and possibly understudied/untested “natural” alternatives) appears to enhance vitamin D metabolism, the importance of consuming adequate levels of vitamin D through diet and supplements cannot be overstated while taking hormones. As indicated by some of the research reviewed, total cholesterol, low-density lipoprotein (LDL) cholesterol, and HDL cholesterol ratios deserve monitoring in the event that vitamin D supplementation might exert a dyslipidemic effect. Again, exercise might be indicated as playing a fundamental role in the comprehensive therapeutic approach. Notably, low serum vitamin D levels have been associated with the incidence of falls in older women,⁸⁵ and vitamin D has been found to be helpful in reducing the incidence of falls, a major factor in fracture risk, by improving muscle strength, walking distance, and functional ability.⁸⁶ Overall, further research is needed to determine the character and full implications of the interaction(s) between supplemental vitamin D and exogenous hormone therapy and their relationship to the many factors influencing bone health and the risks of osteoporosis and fractures.

Heparin, Unfractionated

Heparin, unfractionated (Calciparine, Hepalean, Heparin Leo, Minihep Calcium, Minihep, Monoparin Calcium, Monoparin, Multiparin, Pump-Hep, Unihep, Uniparin Calcium, Uniparin Forte).

Interaction Type and Significance

◇ ≈ **Drug-Induced Adverse Effect on Nutrient Function, Coadministration Therapeutic, with Professional Management**
 ≈ **Drug-Induced Nutrient Depletion, Supplementation Therapeutic, with Professional Management**

Probability:

2. Probable

Evidence Base:

● Consensus

Effect and Mechanism of Action

Over time, heparin causes bone loss, especially in the spine, hips, pelvis, and legs. This effect is more pronounced with standard (unfractionated) heparin (UFH) than with low-molecular-weight heparin (LMWH). At least one mechanism of the negative effect of UFH on bone is nonspecific binding of the longer polysaccharide chains to bone, with inhibition of osteoblastic function. Heparin may also inhibit formation of 1,25-dihydroxyvitamin D by the kidneys.¹²⁶

Research

Majerus et al.¹²⁷ reported that use of heparin, at high doses, for several months causes osteoporosis. Likewise, both Wise and Hall¹²⁸ and later Haram et al.¹²⁹ found that women who received heparin therapy during pregnancy experienced decreased bone density (i.e., osteopenia). On the other hand, in one study, nine women on heparin treatment received 6.46 g daily of a special calcium preparation, ossein-hydroxyapatite compound (OHC) for 6 months and were compared to 11 women not receiving the bone-protective treatment. In the OHC group, good compliance was observed, with no side effects and reduced back pain. Those taking the calcium preparation did not demonstrate the expected decrease in bone mass, and bone mass decreased significantly in the controls.¹³⁰

Nutritional Therapeutics, Clinical Concerns, and Adaptations

Although the adverse effects of heparin on vitamin D and bone metabolism are well documented, research confirming the benefits of supplementing vitamin D and calcium in individuals on heparin therapy for any extended period is limited. However, in the meantime, such nutritional support would most likely be beneficial and is not contraindicated. Physicians prescribing UFH may find it prudent to coadminister with calcium and vitamin D supplementation. With chronic use, the vitamin D metabolite that should be measured to determine vitamin D status is 25(OH)D (25-hydroxyvitamin D), which is the major circulating form of vitamin D, circulating at 1000 times the concentration of 1,25(OH)₂D (1,25-dihydroxyvitamin D) and having a half-life of 2 weeks; after D₃ repletion has been initiated, monitoring 1,25(OH)₂D may be adequate. In some cases, if low, calcitriol may be necessary and appropriate to restore normal activated vitamin D levels; calcitriol is usually required (or appropriate) only in those patients unable to convert 25(OH)D to calcitriol. With long-term heparin therapy, assessment and monitoring of BMD may also be indicated.

Isoniazid and Related Antitubercular Agents

Isoniazid (isonicotinic acid hydrazide, INH; Laniazid, Nydrazid); combination drugs: isoniazid and rifampicin (Rifamate, Rimactane); isoniazid, pyrazinamide, and rifampicin (Rifater). Extrapolated, based on similar properties: Cycloserine (Sermomycin), ethambutol (Myambutol), ethionamide (2-ethylthioisonicotinamide; Ethide, Ethicid, Ethomid, Etomide, Mycotuf, Myobid, Trecator SC), pyrazinamide (PZA; Tebrazid).

See also Rifampin.

Interaction Type and Significance

≈ **Drug-Induced Nutrient Depletion, Supplementation Therapeutic, with Professional Management**

Probability:

2. Probable

Evidence Base:

◎ Emerging

Effect and Mechanism of Action

Research indicates that antituberculous drugs, including isoniazid (INH), induce vitamin D deficiency. Vitamin D levels have been found to be lowered in children with tuberculosis (TB), both in untreated children and in those taking isoniazid. Observed declines in activated vitamin D (1 α ,25-dihydroxyvitamin D) can produce relative hypocalcemia and induce elevation in PTH levels. Isoniazid can inhibit hepatic mixed-function oxidase activity, as evidenced by a reduction in anti-pyrene and cortisol oxidation, as well as hepatic 25-hydroxylase and renal 1 α -hydroxylase; thereby causing such a reduction in the corresponding vitamin D metabolites.^{131,132}

Research

Brodie et al.¹³¹ investigated the effect of isoniazid on vitamin D metabolism, serum calcium and phosphate levels, and hepatic monooxygenase activity by administering isoniazid, 300 mg daily, to eight healthy subjects for 14 days. They observed several responses, including a 47% drop in the concentration of 1 α ,25(OH)₂D (the most active metabolite of vitamin D) after a single dose of isoniazid, with lowered levels continuing throughout the study; declines in levels of 25OHD (the major circulating form of the vitamin) in all subjects and to below normal range in six; and a 36% elevation in PTH levels in response to the relative hypocalcemia produced. In a study

involving 46 children with asymptomatic TB, Toppet et al.¹³³ found that children administered isoniazid for 3 months demonstrated a decrease in blood levels of 1,25(OH)₂D. Isoniazid appears to interfere similarly with the activity of many other nutrients, including magnesium.

Specific evidence is lacking to determine if isoniazid or related agents actually cause symptoms of vitamin D deficiency and calcium depletion, especially with long-term therapy. Clinical trials are warranted to investigate the clinical significance of any depletion pattern and efficacy of prophylactic intervention. Such research is particularly important in children undergoing long-term therapy, in whom potential adverse effects may significantly impair the calcium economy during this critical life stage, when maximum bone density is being attained and will be relied on for life.

Nutritional Therapeutics, Clinical Concerns, and Adaptations

Physicians prescribing isoniazid or related antitubercular therapy, especially for longer than 1 month, are advised to recommend coadministration of vitamin D and calcium, preferably as part of a multivitamin and mineral formulation (at least 50 mg vitamin B₆ daily is indicated with INH as well); this prudent measure is unlikely to interfere with the efficacy of the medication(s). Vitamin D supplementation may be of great value in addition to antituberculous drugs in the treatment of tuberculous children, and its use is highly recommended.¹³⁴ Exposure to sunlight is the simplest and most natural way to provide activated vitamin D; sunshine and mountain air were characteristic of the great TB sanatoriums in the pre-anti-TB drug era. However, when vitamin D is to be supplemented orally, the typical dosage would be in the range of 5 to 10 µg (200-400 IU) per day, depending on size and body weight. Concurrent calcium supplementation in the range of 100 to 250 mg three times daily would be appropriate, but research is lacking to confirm specific effective dosage levels.

Granulomatous lesions, such as those present in extensive TB infection, often contain active 1-hydroxylase enzymes that activate 25-OH-cholecalciferol and are independent of the feedback mechanisms that regulate the renal 1-hydroxylase enzymes. Regular monitoring of serum calcium would reveal early vitamin D toxicity in this setting. Research findings emphasize the need for regular monitoring of 25(OH)D and bone status in this population, even if no sign of rickets is observed in these patients.

Ketoconazole

Ketoconazole (Nizoral).

Interaction Type and Significance

⊕**X** **Bimodal or Variable Interaction, with Professional Management**

Probability:

2. Probable

Evidence Base:

● **Emerging**

Effect and Mechanism of Action

Ketoconazole blocks adrenal steroidogenesis by inhibiting P450 enzymes involved in steroid hormone synthesis. In so doing, however, ketoconazole also inhibits 1α-hydroxylase and 24-hydroxylase, the P450 enzymes that metabolize vitamin D; inhibits renal 1,25(OH)₂D synthesis; and reduces serum levels of calcitriol.^{135,136}

This activity enables ketoconazole to serve as a second-line ADT in the treatment of prostate cancer. The ability of vitamin D to inhibit growth of prostate cancer cells depends on levels

of the active metabolite, 1,25(OH)₂D (calcitriol). Because 24-hydroxylase converts calcitriol to less active products, its inhibition by ketoconazole maintains the magnitude and duration of response to calcitriol.¹³⁷

Research

Adams et al.¹³⁸ reported that ketoconazole decreases the serum 1,25(OH)₂D and calcium concentration in sarcoidosis-associated hypercalcemia. In several studies, Glass et al.¹³⁹⁻¹⁴¹ found that ketoconazole reduced previously elevated serum 1,25(OH)₂D and total serum calcium in hypercalcemic patients, particularly those with sarcoidosis. In a study of 19 patients with well-characterized absorptive hypercalciuria, Breslau et al.¹⁴² found they could separate subjects into those who responded to ketoconazole and those who were nonresponders. Responders demonstrated reduced serum 1,25(OH)₂D, decreased intestinal calcium absorption, and decreased 24-hour urinary calcium excretion.

Nutritional Therapeutics, Clinical Concerns, and Adaptations

Physicians prescribing ketoconazole for extended periods, including use in conjunction with calcitriol for the treatment of prostate cancer, are advised to closely supervise and regularly monitor for drug-induced vitamin D deficiency. Given the nature of ketoconazole's action, simple oral vitamin D supplementation may not provide adequate protection, and calcitriol might need to be prescribed to avoid adverse effects of vitamin D deficiency. Monitoring is essential because the half-life of administered calcitriol tends to be prolonged in presence of ketoconazole.

Neomycin

Neomycin (Mycifradin, Myciguient, Neo-Fradin, NeoTab, Nivemycin); combination drugs: Adcortyl with Graneodin, Betnovate-N, Dermovate-NN, Gregoderm, Synalar N, Tri-Adcortyl, Trimovate.

Interaction Type and Significance

≈≈≈ **Drug-Induced Nutrient Depletion, Supplementation Therapeutic, Not Requiring Professional Management**

◇ **Adverse Drug Effect on Nutritional Therapeutics, Strategic Concern**

Probability:

2. Probable

Evidence Base:

● **Consensus**

Effect and Mechanism of Action

It is widely accepted that extended use of neomycin can significantly decrease absorption or increase elimination of vitamin D as well as many other nutrients, including beta-carotene, folic acid, vitamin A, vitamin B₁₂, vitamin K, calcium, iron, magnesium, potassium, and sodium.⁸⁹

Research

No specific evidence is cited because the literature treats this interaction as axiomatic.

Nutritional Therapeutics, Clinical Concerns, and Adaptations

Physicians prescribing extended courses of neomycin are advised to coadminister a multivitamin and mineral supplement as a prudent measure to avoid potential drug-induced deficiencies. Separation of oral intake by at least 2 hours will reduce the risk of interference with absorption of either preparation.

Orlistat

Orlistat (alli, Xenical).

Interaction Type and Significance

≈≈≈ **Drug-Induced Nutrient Depletion,
Supplementation Therapeutic, Not Requiring
Professional Management**

Probability:

2. Probable

Evidence Base:

○ Preliminary

Effect and Mechanism of Action

Orlistat is a gastrointestinal lipase inhibitor that binds dietary fat and prevents its absorption. Such activity can interfere with the absorption of vitamin D and other fat-soluble nutrients and potentially induce deficiency patterns.

Research

In a 52-week, double-blind, randomized, parallel-group, placebo-controlled multicenter study, preceded by a 4-week, single-blind, placebo run-in period, James et al.¹⁴³ observed that vitamin D (and beta-carotene) concentrations decreased in patients treated with 120 mg orlistat three times daily, compared with those receiving placebo (even though fat-soluble vitamin levels remained within the normal range in the treatment group). Van Gaal et al.¹⁴⁴ conducted a 6-month, multicenter, randomized, double-blind, parallel-group clinical trial involving 676 obese men and women. Most subjects demonstrated reduced blood levels of vitamins D and A, but these remained within the clinical reference ranges, and only few individuals developed nutrient deficiency patterns that required supplementation. However, in a clinical trial involving 17 obese African-American and Caucasian adolescents receiving orlistat, 120 mg three times daily, McDuffie et al.¹⁴⁵ observed several significant nutrient depletion patterns despite coadministration of a daily multivitamin supplement containing vitamin A (5000 IU), vitamin D (400 IU), vitamin E (300 IU), and vitamin K (25 µg). In particular, mean serum levels of vitamin D were significantly reduced compared with baseline after 1 month of orlistat, despite multivitamin supplementation.

Nutritional Therapeutics, Clinical Concerns, and Adaptations

Predictably, in view of its known pharmacological effects, orlistat interferes with absorption of fat-soluble nutrients, including vitamin D. The question of whether, and for which individuals, the probable decline in vitamin D blood level reaches a threshold of clinical significance remains unclear and worthy of further clinical trials. Pending conclusive research findings, physicians prescribing orlistat for 6 months or longer are advised to err on the side of prudence and coadminister supplemental vitamin D (and possibly vitamin A), potentially in the form of a moderate-dosage multivitamin combination. Separating intake of orlistat and supplemental nutrients by 2 or more hours may reduce adverse effects on absorption. Notably, the U.S. Food and Drug Administration (FDA) requires that food products containing olestra, which also inhibits fat absorption, include vitamin D and other fat-soluble vitamins (i.e., vitamins A, E, and K).

Raloxifene

Raloxifene (Evista).

Interaction Type and Significance

⊕⊕ **Beneficial or Supportive Interaction, with
Professional Management**

Probability:

2. Probable

Evidence Base:

○ Preliminary

Effect and Mechanism of Action

The ability of raloxifene, a selective estrogen receptor modifier (SERM) that is an analog of tamoxifen, to inhibit bone resorption and maintain or increase BMD depends on calcium nutrition and vitamin D's role in enabling calcium absorption and bone metabolism. Vitamin D can increase effectiveness of the drug.

Research

Boivin et al.¹⁴⁶ found that the coadministration of calcium (500 mg) and vitamin D₃ (400-600 IU) with raloxifene increased the degree of mineralization of bone in postmenopausal women, as demonstrated by iliac crest biopsies. All currently approved bone-active pharmacological agents have been studied only in conjunction with supplemental calcium, and newer anabolic agents increase mineral demand in skeletal tissue and will thus require even higher levels of calcium repletion.⁷⁸

Nutritional Therapeutics, Clinical Concerns, and Adaptations

Calcium and vitamin D are essential for maintaining bone mass and density and imperative to the success of drug therapies for inducing bone augmentation.⁷⁷ Deficiencies of both nutrients are common in the patient populations at highest risk for osteoporosis. The importance of exercise and sound nutrition (including adequate protein and phosphorus intake) as foundational cannot be overemphasized and is supported by growing evidence. Calcium has a clearly demonstrated effect of enhancing estrogen's effects on bone metabolism. Further, most research indicates that consistent exposure to sunlight provides a safe and effective, as well as otherwise beneficial, method of elevating vitamin D levels. Doses of 1500 mg calcium and 800 IU vitamin D daily provide prudent nutritional support for osteoporosis prevention and treatment.

Thus, a synergistic combination of oral calcium and vitamin D, within the context of an active lifestyle, constitutes the core proactive intervention within integrative therapeutics for all individuals at high risk for osteoporosis, or a foundational treatment for diagnosed bone loss. Notably, low serum vitamin D levels have been associated with the incidence of falls in older women,⁸⁵ and vitamin D has been found to be helpful in reducing the incidence of falls, a major factor in fracture risk, by improving muscle strength, walking distance, and functional ability.⁸⁶ Also, hormone supplementation or replacement regimens (conventional HRT, bio-identical estrogens/progesterone, herbal hormone precursors/modulators) should be considered if indicated in women.

In addition to these primary and secondary therapies, the use of raloxifene in postmenopausal women can provide a potent intervention in reversing bone loss and supporting healthy bone mass, although it does tend to increase, rather than decrease, menopausal symptoms. Raloxifene may also be useful in reducing the risk of breast cancer in this population.

Rifampin

Rifampin (Rifadin, Rifadin IV); combination drugs: isoniazid and rifampicin (Rifamate, Rimactane); isoniazid, pyrazinamide, and rifampicin (Rifater).

See also Isoniazid section.

Interaction Type and Significance

- ≈≈ **Drug-Induced Nutrient Depletion, Coadministration Therapeutic, with Professional Management**
- ◇≈≈ **Drug-Induced Adverse Effect on Nutrient Function, Coadministration Therapeutic, with Professional Management**

Probability:

2. Probable

Evidence Base:

○ Preliminary

Effect and Mechanism of Action

Pharmacokinetic interaction occurs because rifampin is a potent inducer of hepatic drug metabolism, specifically (cytochrome P450) 2C9, 2C19, and 3A4. Rifampin inhibits CYP1A2 and increases oxidation of antipyrine and 6β-hydroxycortisol, potentially causing decreased plasma levels of 25-hydroxycholecalciferol (25-OHD), which represents the body stores of active vitamin D precursor.¹⁴⁷

Research

In a small study with eight male subjects, Brodie et al.¹⁴⁷ found that a 2-week course of rifampicin (600 mg/day orally) produced a consistent fall in plasma 25-OHD levels of approximately 70%. Within the time frame of the study, plasma levels of 1,25-dihydroxycholecalciferol, PTH, and calcitonin were not significantly altered.

Nutritional Therapeutics, Clinical Concerns, and Adaptations

Physicians prescribing rifampicin for extended periods would be prudent to coadminister supplemental vitamin D at a dosage level appropriate to the patient's age, weight, sun exposure, and other characteristics and needs. Regular monitoring of 25-OHD would be appropriate.

Thiazide Diuretics

Bendroflumethiazide (bendrofluazide; Naturetin); combination drug: bendrofluazide and propranolol (Inderex); benzthiazide (Exna), chlorothiazide (Diuril), chlorthalidone (Hygroton), cyclopenthiazide (Navidrex); combination drug: cyclopenthiazide and oxprenolol hydrochloride (Trasidrex); hydrochlorothiazide (Aquazide, Esidrix, Ezide, Hydrocot, HydroDiuril, Microzide, Oretic); combination drugs: hydrochlorothiazide and amiloride (Moduretic); hydrochlorothiazide and captopril (Acezide, Capto-Co, Captozide, Co-Zidocapt); hydrochlorothiazide and enalapril (Vaseretic); hydrochlorothiazide and lisinopril (Prinzide, Zestoretic); hydrochlorothiazide and losartan (Hyzaar); hydrochlorothiazide and metoprolol (Lopressor HCT); hydrochlorothiazide and spironolactone (Aldactazide); hydrochlorothiazide and triamterene (Dyazide, Maxzide), hydroflumethiazide (Diu-cardin), methyclothiazide (Enduron), metolazone (Zaroxolyn, Mykrox), polythiazide (Renese), quinethazone (Hydromox), trichlormethiazide (Naqua).

Interaction Type and Significance

- ◇◇ **Drug-Induced Effect on Nutrient Function, Supplementation Contraindicated, Professional Management Appropriate**
- XX **Minimal to Mild Adverse Interaction—Vigilance Necessary**

Probability:

5. Improbable

Evidence Base:

□ Inadequate

Effect and Mechanism of Action

Thiazide diuretics induce changes in renal tubules that reduce calcium excretion and could potentially lead to hypercalcemia in rare instances and changes in vitamin D metabolism (particularly increases in serum levels of 24,25-dihydroxycholecalciferol).

Research

Riis and Christiansen¹⁴⁸ studied the actions of bendroflumethiazide (5 mg/day), along with 500 mg/day calcium, on vitamin D metabolism in a 12-month, placebo-controlled clinical trial in 19 healthy, early-postmenopausal women. Subjects in the thiazide group demonstrated a significant elevation in the serum concentration of 24,25-dihydroxycholecalciferol and a tendency toward decreased serum 1,25-dihydroxycholecalciferol, although mean serum 25-hydroxycholecalciferol remained unchanged.

Nutritional Therapeutics, Clinical Concerns, and Adaptations

Given the uncertain implications of such findings, physicians are advised to closely supervise and regularly monitor serum calcium levels when prescribing thiazide diuretics. Special testing before initiating or increasing any vitamin D supplementation is probably unnecessary.

Thioridazine

Thioridazine (Mellaril).

Interaction Type and Significance

- XXX **Potentially Harmful or Serious Adverse Interaction—Avoid**

Probability:

2. Probable

Evidence Base:

● Consensus

Effect and Mechanism of Action

Cholecalciferol (vitamin D₃), as a cytochrome P2D6 inhibitor, may decrease the metabolism of thioridazine via CYP isoenzymes.

Research

In a double-blind, randomized-order, crossover study of thioridazine pharmacodynamics, Hartigan-Go et al.¹⁴⁹ used debrisoquin, an agent presumed to be extensively metabolized by CYP2D6, to determine the hydroxylation status of thioridazine. They also found that thioridazine can prolong QTc intervals in a dose-dependent manner in normal subjects.¹⁴⁹ Furthermore, a manufacturer of thioridazine determined that the peak concentration (C_{max}) of thioridazine (single oral dose of 25 mg) is highly variable, and that some individuals are "slow hydroxylators" and others are "rapid hydroxylators." In regard to the effects of CYP2D6 inhibition, compared with placebo, thioridazine increased QTc intervals by 9 msec and 23 msec with 10-mg and 50-mg doses, respectively.¹⁵⁰

Clinical Implications and Adaptations

Concomitant use of thioridazine and agents that inhibit CYP2D6 isoenzymes such as cholecalciferol is contraindicated and should be avoided. Evidence is lacking to suggest that supplementation with forms of vitamin D other than cholecalciferol (vitamin D₃) is problematic, and vitamin D support is often important in patients being treated with thioridazine.

Alternatives to thioridazine may need to be considered when supplementation with vitamin D₃ is critical to a patient's medical needs and central to the therapeutic strategy for their comprehensive care. Regardless, an alternate drug choice may

be necessary because this phenothiazine antipsychotic has been withdrawn from the market in many jurisdictions.

Verapamil and Related Calcium Channel Blockers

Evidence: Verapamil (Calan, Calan SR, Covera-HS, Isoptin, Isoptin SR, Verelan, Verelan PM).

Extrapolated, based on similar properties: Amlodipine (Norvasc); combination drug: amlodipine and benazepril (Lotrel); bepridil (Bapadin, Vascor), diltiazem (Cardizem, Cardizem CD, Cardizem SR, Cartia XT, Dilacor XR, Diltia XT, Tiamate, Tiazac), felodipine (Plendil); combination drugs: felodipine and enalapril (Lexxel); felodipine and ramipril (Triapin); gallopamil (D600), isradipine (DynaCirc, DynaCirc CR), lercanidipine (Zanidip), nicardipine (Cardene, Cardene I.V., Cardene SR), nifedipine (Adalat, Adalat CC, Nifedical XL, Procardia, Procardia XL); combination drug: nifedipine and atenolol (Beta-Adalat, Tenif); nimodipine (Nimotop), nisoldipine (Sular), nitrendipine (Cardif, Nitrepin), verapamil combination drug: Verapamil and trandolapril (Tarka).

Interaction Type and Significance

XXX Potentially Harmful or Serious Adverse Interaction—Avoid

◇◇◇ **Impaired Drug Absorption and Bioavailability, Avoidance Recommended**

◇◇ **Drug-Induced Effect on Nutrient Function, Supplementation Contraindicated, Professional Management Appropriate**

Probability:

5. Improbable

Evidence Base:

○ **Preliminary**

Effect and Mechanism of Action

Verapamil is a calcium antagonist, whereas vitamin D facilitates calcium absorption and metabolism. An interaction involving supplemental vitamin D, due to pharmacodynamic antagonism, is theoretically plausible but considered improbable. Vitamin D (or calcium) supplementation could potentially interfere with the primary activity of verapamil, and thus its therapeutic effectiveness, by increasing calcium availability. Further, hypercalcemia induced by toxic levels of vitamin D may precipitate cardiac arrhythmia in patients taking verapamil, although this is extremely rare, if it ever occurs. Conversely, verapamil may decrease endogenous production of vitamin D. Verapamil may also induce target-organ parathyroid hormone (PTH) resistance.

Research

The evidence for this interaction is minimal, but it is often considered self-evident. In a 1982 *in vitro* study, Lerner and Gustafson¹⁵¹ reported that verapamil inhibited 1 α -hydroxyvitamin D₃—stimulated bone resorption in tissue culture. In an animal model using rats fed a high-calcium diet, Fox and Della-Santina¹⁵² found that chronic oral verapamil administration decreased 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃] levels (by reducing production) and increased plasma immunoreactive PTH (most likely by inducing target-organ PTH resistance). In contrast, verapamil produced no significant effect on 1,25(OH)₂D₃ levels in rats fed a low-calcium diet.

Reports

Bar-Or and Gasiel¹⁵³ reported that calcium adipate and calciferol antagonized the heart rate-limiting effect of verapamil in a patient being treated for atrial fibrillation.

Clinical Implications and Adaptations

Physicians prescribing verapamil or other calcium channel blockers are advised to exercise caution regarding the concomitant use of vitamin D. This possible interaction can present strategic concerns because many patients receiving verapamil may also have or be at risk for osteoporosis, such that calcium and vitamin D support is an important concomitant need. For example, Holick¹⁵⁴ suggests that such patients typically need vitamin D support. Close supervision and regular monitoring, preferably within the context of integrative care involving health care professionals trained and experienced in both conventional pharmacology and nutritional therapeutics, are essential in cases where concurrent use of verapamil and vitamin D is clinically appropriate. In cases of overdose with verapamil or other calcium channel blockers, intravenous calcium chloride or gluconate is the treatment of choice.

Related Discussion

Calcitriol and Vitamin D Analogs

Alfacalcidol, calcitriol, dihydrotachysterol.

Investigations into the pharmacology and clinical application of 1,25(OH)₂D₃, the hormonal active form of vitamin D, have proceeded far beyond those of the nutrient itself. In many situations, including adverse drug-induced effects on vitamin D metabolism, calcitriol has been administered to increase effective activated vitamin D levels. In some recent research and emerging clinical protocols, calcitriol has been used as a central component of the pharmacological repertoire, that is, as a drug and not as a nutrient.

Stio et al.¹⁵⁵ demonstrated synergistic immunoregulatory properties and inhibitory effect of cyclosporine A and vitamin D derivatives on T-lymphocyte proliferation in T lymphocytes prepared from ulcerative colitis patients. Such an alternative therapeutic approach in these patients could reduce the dose, and consequently the toxicity, of cyclosporine A. In an animal model using mice with breast tumor xenografts, Sundaram et al.¹⁵⁶ found that treatment with a vitamin D₃ analog, EB 1089, before ionizing radiation reduces tumor growth and induces apoptosis, without inducing hypercalcemia. In another *in vitro* experiment, Dunlap et al.¹⁵⁷ reported that treating human prostate cancer cells with calcitriol and its analog, 19-nor-1 α ,25(OH)₂D₂, may potentiate the effects of ionizing radiation and make these cells more susceptible to the effects of radiotherapy.

In a phase II clinical trial, Beer et al.¹⁵⁸ demonstrated that coadministration of high-dose calcitriol to weekly treatment with the chemotherapy agent docetaxel (Taxotere) appears to improve the therapeutic response in men with hormone-refractory prostate cancer without compromising safety, with the combination providing as much as twice the efficacy as docetaxel alone, as measured by prostate-specific antigen (PSA) response rate. Subjects received oral calcitriol, 0.5 μ g/kg, on the first day of the treatment cycle, followed by an infusion of docetaxel, 36 mg/m², on the following day. This sequence was repeated weekly for 6 weeks of an 8-week cycle until there was evidence of disease progression or unacceptable toxicity, or until the patient requested to be withdrawn from the study. The phase III, randomized clinical trials following from this study evaluate the use of weekly docetaxel versus weekly docetaxel plus calcitriol in hormone-refractory prostate cancer.

THEORETICAL, SPECULATIVE, AND PRELIMINARY INTERACTIONS RESEARCH, INCLUDING OVERSTATED INTERACTIONS CLAIMS

Antacids, Especially Magnesium-Containing Antacids

Aluminum carbonate gel (Basajel), aluminum hydroxide (Alternagel, Amphojel); combination drugs: aluminum hydroxide, magnesium carbonate, alginic acid, and sodium bicarbonate (Gaviscon Extra Strength Tablets, Gaviscon Regular Strength Liquid, Gaviscon Extra Strength Liquid); aluminum hydroxide and magnesium hydroxide (Advanced Formula Di-Gel Tablets, co-magaldrox, Di-Gel, Gelusil, Maalox, Maalox Plus, Mylanta, Wingel); aluminum hydroxide, magnesium trisilicate, alginic acid, and sodium bicarbonate (Alenic Alka, Gaviscon Regular Strength Tablets); calcium carbonate (Titalac, Tums), magnesium hydroxide (Phillips' Milk of Magnesia MOM); combination drugs: magnesium hydroxide and calcium carbonate (Calcium Rich Roloids); magnesium hydroxide, aluminum hydroxide, calcium carbonate, and simethicone (Tempo Tablets); magnesium trisilicate and aluminum hydroxide (Adcomag trisil, Foamicon); magnesium trisilicate, alginic acid, and sodium bicarbonate (Alenic Alka, Gaviscon Regular Strength Tablets); combination drug: sodium bicarbonate, aspirin, and citric acid (Alka-Seltzer).

Chronic use of some antacids may alter availability, levels, and metabolism of vitamin D. Evidence is lacking to confirm this potential interaction or determine its patterns of clinical significance.

Calcitonin

Calcitonin

The effect of calcitonin (clinically used primarily for treatment of hypercalcemia, but also osteoporosis and painful bone metastases, especially of multiple myeloma) may be antagonized by supplemental vitamin D.

Digoxin

Digoxin (Digitek, Lanoxin, Lanoxicaps, purgoxin).

Vitamin D enhances calcium absorption and elevated calcium levels may potentiate the effects of digoxin and contribute to increased risk of digoxin toxicity, potentially precipitating cardiac arrhythmia. At toxic levels, vitamin D could aggravate hypercalcemia and increase adverse effects of digoxin. Conversely, digoxin can potentiate the arrhythmogenic effects of hypercalcemia, leading to a symptomatic rhythm disorder.¹⁵⁹

Although pharmacologically plausible, evidence from clinical studies regarding a direct interaction between digoxin and supplemental vitamin D is lacking. The risks associated with elevated or unstable calcium levels in patients receiving digoxin therapy are well known.

Most cases of hypercalcemia are unrelated to vitamin D intake. Vitamin D toxicity from supplemental sources is uncommon, if not rare, and would usually require an extended period of excessive vitamin D intake. However, even though rare, hypercalcemia would be a characteristic of hypervitaminosis D and would carry a significant probability of clinical significance in an individual undergoing digoxin therapy.

The combined use of vitamin D and digoxin may be therapeutically appropriate but involves judicious prescribing, cautious scrutiny, and careful follow-up. In particular, close supervision and regular monitoring of calcium levels are appropriate and prudent when prescribing digoxin therapy, especially in conjunction with any agents that might alter calcium status. The probability of an adverse reaction is generally quite low, but the consequences of such an event could potentially be

severe and rapid in onset once a critical mass (hypervitaminosis D, hypercalcemia) had been reached. Physicians and other health care practitioners are advised to discuss use of and create an inventory of herbs and nutritional supplements with their patients in a respectful yet frank dialogue. Vitamin D excess to the degree that could cause hypercalcemia through sun exposure is generally considered impossible.

Doxorubicin

Doxorubicin (Adriamycin, Rubex).

Supplemental vitamin D may enhance the effects of doxorubicin. Given the positive trend in the findings from studies investigating the coadministration of calcitriol with a range of conventional cancer therapies, this potential supportive interaction warrants clinical trials. In an *in vitro* experiment, Ravid et al.¹⁶⁰ found that 1,25(OH)₂D₃ may enhance the susceptibility of breast cancer cells to doxorubicin-induced oxidative damage.

Flurbiprofen

Flurbiprofen (Ansaid).

Through its primary mechanism of prostaglandin synthetase inhibition or possibly through other activities, flurbiprofen appears to reduce calcium and vitamin D levels in individuals with hypercalcemia. Buck et al.¹⁶¹ found that flurbiprofen reduced circulating 1,25(OH)₂D in patients with recurrent calcium lithiasis. In a double-blind study, Brown et al.¹⁶² reported on an individual with sarcoidosis in whom flurbiprofen reduced plasma calcium levels and urinary hydroxyproline excretion to normal, while plasma 1,25(OH)₂D₃ remained high. Clinical trials are warranted to determine whether flurbiprofen might influence calcium and vitamin D levels in healthy subjects or individuals with conditions involving other calcium and vitamin D metabolic disorders.

Hydroxychloroquine

Hydroxychloroquine (Plaquenil).

In a case report, Barré et al.¹⁶³ stated that 24 weeks of treatment with hydroxychloroquine reversed hypercalcemia and returned calcium and 1,25(OH)₂D levels to normal in a 45-year-old woman with sarcoidosis undergoing hemodialysis. The authors noted that these findings demonstrated the capacity of hydroxychloroquine to inhibit the conversion of 25(OH)D to 1,25(OH)₂D and suggested "the efficacy of hydroxychloroquine as an alternate to corticosteroids in the treatment of hypercalcemia of granulomatous disease." Controlled clinical trials are warranted to follow up on this report and also to determine whether hydroxychloroquine might beneficially influence calcium and vitamin D levels in healthy subjects or individuals with conditions other than sarcoidosis. Pending clarification by such research, physicians prescribing hydroxychloroquine are advised to discuss the potential effects of calcium and vitamin D supplementation with patients and closely supervise and regularly monitor calcium and vitamin D status in individuals for whom such supplementation may be appropriate for comorbid conditions.

Indapamide

Indapamide (Lozol).

Indapamide is a thiazide-like diuretic, but evidence is lacking as to whether it might enhance the activity of vitamin D in the manner of thiazide diuretics and whether such interaction might rise to the level of clinical significance. Pending clarification by controlled clinical trials, physicians prescribing indapamide are advised to discuss the potential effects of vitamin D supplementation with patients and closely supervise and

regularly monitor calcium and vitamin D status in individuals for whom such supplementation may be appropriate for comorbid conditions.

Mineral Oil

Mineral Oil (Agoral, Kondremul Plain, Liquid Parafin, Milkinol, Neo-Cultol, Petrogalar Plain).

Mineral oil, as a lipid solvent, interferes with normal absorption of vitamin D (and other nutrients) and increases its elimination from the body. Some disagreement surrounds the degree of clinical significance, particularly with regard to vitamin D in particular, but most research has found that mineral oil interferes with the absorption of many nutrients, including beta-carotene, calcium, phosphorus, potassium, and vitamins A, D, K, and E. Chronic use of mineral oil can cause a deficiency of vitamins A, D, E, and K.¹⁶⁴

If mineral oil is used for any extended period, concomitant administration of a multivitamin and mineral supplement would be generally be advisable. Malabsorption of fat-soluble vitamins due to ingestion of mineral oil can be minimized by administering mineral oil on an empty stomach or consuming vitamin or mineral supplements at least 2 hours before or after the mineral oil. In general, it is advisable to limit the internal use of mineral oil to less than 1 week.

Sodium Fluoride

Sodium Fluoride (Fluorigard, Fluorinse, Fluoritab, Fluorodex, Flura-Drops, Flura-Tab, Karidium, Luride, Pediaflor, PreviDent).

In an in vitro experiment using serum-free cultures of human marrow, stromal osteoblast-like cells, Kassem et al.¹⁶⁵ found that $1,25(\text{OH})_2\text{D}_3$ potentiated fluoride-enhanced type I collagen production in a dose-dependent way (as well as production of ALP and osteocalcin), compared with sodium fluoride alone, which did not increase type I collagen production. Controlled clinical trials would be necessary to determine if coadministration of $1,25(\text{OH})_2$ -cholecalciferol and sodium fluoride might promote beneficial collagen growth.

Sucralfate

Sucralfate (Carafate).

In a multiclinical and randomized study involving 100 patients with chronic gastric ulcer, Patty et al.¹⁶⁶ reported that sucralfate may reduce intestinal absorption of vitamin D. However, in a clinical trial of 30 patients with chronic renal failure on intermittent hemodialysis, Vucelic et al.¹⁶⁷ found that sucralfate intake was associated with slight increases in serum calcium levels. Physicians prescribing sucralfate are advised to discuss the possible implications of vitamin D (and calcium) supplementation with patients for whom such nutrition is important to strategic clinical goals and to monitor vitamin D and calcium levels regularly should supplementation be deemed appropriate.

Warfarin

Warfarin (Coumadin, Marevan, Warfilone).

Based on a single letter published in *JAMA* (1975), concern has been raised about a possible adverse interaction between vitamin D and anticoagulant medicines such as warfarin.¹⁶⁸ The potential for increased activity of anticoagulants due to vitamin D has not been confirmed by other case reports or any substantial clinical research. Physicians prescribing warfarin should be aware of rumors arising from recurring reference to this warning of theoretical risk of enhanced drug activity from vitamin D supplementation. Even though the occurrence of

this interaction would seem to be widespread if it represented a significant risk, given the widespread use of vitamin D, health care professionals are advised to discuss this theoretical concern, and the lack of evidence supporting it, with patients before initiating supplementation with vitamin D in doses greater than 10 µg (400 IU) daily. Nevertheless, in conventional practice, vitamin D supplementation at usual dosages is not considered contraindicated during anticoagulant therapy. In general, because warfarin interacts with such a wide variety of substances, it is wise to monitor the prothrombin time (PT) twice weekly when new medications or nutrients that are to be administered for more than a few days are added to the patient's regimen. Only in recent years have the profound interactions between warfarin and acetaminophen and between warfarin and cranberry juice been identified. There are likely many such interactions that are yet unrecognized. Frequent monitoring of the PT/INR when diet, medication, or nutrient regimens are changed is the best protection against untoward clinical events occurring from such as-yet unrecognized interactions, especially those that may occur only in patients with certain genetic polymorphisms.

NUTRIENT-NUTRIENT INTERACTIONS

Boron

Boron appears to play a significant role in converting vitamin D from 25-OHD to its active form $[1,25(\text{OH})_2\text{D}]$, thus facilitating calcium absorption. This observation is clinically relevant because it supports the practice of using supplemental vitamin D₃ with boron, rather than calcitriol, thereby avoiding the high costs of calcitriol.

After examining animal nutrition models, Hunt¹⁶⁹ concluded that dietary boron alleviates perturbations in mineral metabolism characteristic of vitamin D₃ deficiency. Hunt et al.¹⁷⁰ found that dietary boron modifies the effects of vitamin D₃ nutrition on indices of energy substrate utilization and mineral metabolism in the chick. For example, chicks fed a diet containing insufficient vitamin D for 26 days exhibited decreased food consumption and plasma calcium concentrations, as well as increased plasma concentrations of glucose, β-hydroxybutyrate, triglycerides, triiodothyronine (T₃), cholesterol, and alkaline phosphatase (ALP) activity. After administration of boron, plasma glucose and triglycerides returned to concentrations exhibited by chicks that had been fed a diet adequate in vitamin D. Such findings support the coadministration of boron and vitamin D₃ as a potentially useful strategy in diabetes management. Likewise, boron elevated the numbers of osteoclasts and alleviated malformation of the marrow sprouts of the proximal tibial epiphyseal plate in rachitic (vitamin D-deficient) chicks, thus correcting a distortion characteristic of vitamin D₃ deficiency.¹⁷¹ In an experiment investigating the effects of dietary boron in rats fed a vitamin D-deficient diet, Dupre et al.¹⁷² observed that introduction of boron into the diet resulted in higher apparent-balance values of calcium, magnesium, and phosphorus.

In a study involving male subjects over 45 years of age and postmenopausal women fed a low-magnesium and low-copper diet, Nielsen et al.¹⁷³ showed that administration of 3.25 mg of boron daily increased levels of plasma vitamin D₂.

Caffeine

Rapuri et al.¹⁷⁴ found that elderly women with high caffeine intakes had significantly higher rates of bone loss at the spine than those with low intakes, and that caffeine intake interacts

with vitamin D receptor (VDR) genotypes. Nevertheless, the role of caffeine as a risk factor for bone loss remains controversial.

Calcium

Coadministration of vitamin D and calcium, along with weight-bearing exercise and sunlight exposure, are generally considered the foundational approaches to calcium nourishment, attainment, and maintenance of bone mineral density (BMD) and prevention of bone loss.¹⁷⁵⁻¹⁷⁷ A normal physiological function of vitamin D is to facilitate intestinal calcium absorption.

Although findings have varied, often significantly influenced by methodology (especially in meta-analyses), most research indicates that concomitant intake of vitamin D and calcium reduces risk of fractures and enhances bone health, particularly for individuals with a preexisting insufficiency and with consistent patient compliance. In general, according to Heaney and Weaver,⁷⁸ prudent nutritional support for osteoporosis prevention and treatment consists of 30 to 40 mmol calcium per day together with sufficient vitamin D to maintain serum 25(OH)D levels above 80 nmol/L (~25 µg or 1000 IU vitamin D daily).⁷⁸ In a Cochrane Library review of 38 randomized or quasirandomized trials, Avenell and Handoll¹⁷⁸ found that the risk of fractures of the hip and other nonspinal bones was reduced slightly in elderly people who are frail and at risk for bone fractures, particularly those who live in nursing homes or other institutions, if vitamin D and calcium were given. Nevertheless, the risk of spinal fractures did not appear to be reduced.

In a trial involving 944 healthy Icelandic adults, Steingrimsdottir et al.⁴¹ found that with 25-OHD levels below 10 ng/mL (i.e., significant vitamin D deficiency), maintaining calcium intake above 800 mg/day appeared to normalize calcium metabolism, as determined by the PTH level, but in individuals with higher 25-OHD levels, no benefit was observed from calcium intake greater than 800 mg/day.

In 2005 and 2006, three major papers were published discussing the relationship between calcium, vitamin D, and osteoporotic fracture risk. Findings from the RECORD study (*The Lancet*, 2005) suggested a lack of benefit from concomitant calcium and vitamin D in the prevention of fractures in menopausal women.³⁹ Subsequently, Jackson et al.⁴² (2006) used data from the Women's Health Initiative that questioned the assumption that calcium and vitamin D can prevent osteoporosis-related hip fractures. They randomly assigned 36,000 postmenopausal women to receive elemental calcium, as calcium carbonate (500 mg twice daily), plus vitamin D (200 IU twice daily) or a placebo for an average of 7 years. Notably, the average calcium consumption in both groups was approximately 1150 mg/day, close to the appropriate recommended intake level. After 7 years, subjects in the treatment group exhibited 12% fewer hip fractures than those in the placebo group, a finding that was not statistically significant. However, a deeper analysis of the data reveals that more significant differences

appear when considering compliance and initial calcium intake levels. For example, on excluding women who were not adhering to the program, the reduction in fractures was greater, with 29% fewer fractures in the treatment group than in the placebo group, a statistically significant difference. Likewise, hip fracture risk decreased by about 22% in treated subjects whose initial calcium intake was low or moderate.⁴² Overall, in both trials, compliance was only about 40% and 50%.

In contrast, Boonen et al.¹⁷⁹ conducted a multifaceted meta-analysis of major randomized, placebo-controlled trials that analyzed the effects of vitamin D alone or in combination with calcium. In one analysis they found that randomized clinical trials comparing vitamin D alone to placebo showed no effect. Likewise, a subsidiary analysis showed that low doses of vitamin D (< 800 units/day) exerted no effect. However, they demonstrated a statistically significant 21% reduction in risk of fracture, compared with placebo, among subjects receiving 800 IU vitamin D and more than 1000 mg calcium daily. The authors concluded that vitamin D exerts its beneficial effect on bone predominantly by increasing absorption of calcium.

In some individuals and with certain medical conditions, supplementation with vitamin D, particularly at excessive levels, can induce an excessive increase in the absorption of calcium and increase the risk of hypercalcemia and kidney stone formation.⁴² The risk of such adverse effects may be influenced by the form of calcium used, as well as other, individual patient variables.

Phosphorus

Vitamin D may cause an increase in the absorption of phosphorus. The clinical implications of this potential pattern of interaction have yet to be fully investigated in controlled human trials.

Sodium

In a small clinical trial involving 11 normal subjects and two patients with postsurgical hypoparathyroidism, Breslau et al.¹⁸⁰ found that in normal subjects, sodium-induced renal hypercalciuria is accompanied by increased 1,25(OH)₂D synthesis and enhanced intestinal calcium absorption. Since this adaptive mechanism did not occur in two patients with hypoparathyroidism, the authors suggested that mediation of this effect by parathyroid hormone was possible.

Vitamin A

Vitamin A antagonizes some of the activity of vitamin D. High doses of vitamin A, given concurrently with vitamin D, tend to reduce the toxic effects of vitamin D.^{181,182} Vitamin A toxicity, such as hepatotoxicity, must also be considered in such contexts.

The 182 citations for this monograph, as well as additional reference literature, are located under Vitamin D (Calciferol) on the CD at the back of the book.

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