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Vitamin D Deficiency: "At Risk" Patient Populations and Potential Drug Interactions

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Abstract

Vitamin D is known to play an essential role in calcium homeostasis; however, excessive amounts can have harmful effects. Calcium and vitamin D levels are known to be influenced by drug interactions and pathology ranging from cancer to cardiovascular disease. Vitamin D supplementation has become widespread, and it is important for clinicians to understand the way that certain conditions and medications interact with vitamin D and calcium homeostasis. The purpose of this review is to outline the benefits and adverse effects of vitamin D and how its levels are affected by certain pathologic and pharmacologic interactions.

Keywords: Vitamin D, drug interactions, disease interactions, calcium homeostasis

Introduction

The supplementation of vitamin D has become an exciting topic, as research has shown the molecule to play an important role in many physiologic processes. However, excess vitamin D has been found to have negative effects, and vitamin D levels are known to be altered by certain disease processes and drug interactions. The purpose of this review is to outline the benefits and adverse effects of vitamin D and how its levels are affected by certain pathologic and pharmacologic interactions.

Vitamin D, Calcium, and Phosphate Metabolism

Plasma calcium concentration is among the most closely regulated of all physiologic processes in the body, with fluctuations of only 1-2% on a daily basis. Ionized calcium is involved in numerous biochemical processes including the maintenance of membrane stability, neurotransmitter release, stimulus-secretion coupling, signal transduction, and enzyme activation. Additionally, calcium (along with phosphate) is the major inorganic constituent of bone. (1)

Abnormal calcium levels can lead to a multitude of physiological and biochemical problems in the body. Hypercalcaemia, an increase in serum ionized calcium, can cause depression of central and peripheral neurons leading to sluggishness and hyporeflexia. Additionally, elevated calcium may lead to metastatic calcification, resulting in precipitation of calcium phosphate in tissues. Contrarily, hypocalcaemia can increase the membrane permeability of sodium, eventually leading to the generation of spontaneous action potentials in neurons, cardiac, and skeletal muscle leading to hypocalcemic tetany or arrhythmias. (2)

Ninety-nine percent of total body calcium is sequestered in the skeleton, while the remaining calcium is either intracellular (0.9%) or extracellular (0.1%). Calcium can exist in three forms in human plasma. The ionized form is biologically active and accounts for 50% of blood calcium, while 40% of calcium is bound to plasma proteins, and the remaining 10% is in the form of soluble complexes. (3) Phosphate is mostly ionized in plasma in the form of phosphoric acid (inorganic phosphate). There are three organ systems involved in maintaining calcium and phosphate homeostasis: the gastrointestinal tract, the skeleton, and the kidneys. These organ systems are acted on by hormones that function to tightly regulate circulating levels of calcium and phosphate; these hormones include parathyroid hormone (PTH), 1, 25 dihydroxyvitamin D (calcitriol), and calcitonin. (1)

PTH is produced by the chief cells of the parathyroid glands and is an important regulator of plasma calcium and phosphate. Hypocalcemia prompts a release of PTH from the parathyroids, whereas release is inhibited by hypercalcemia and calcitriol. A calcium sensing receptor on the plasma membrane of chief cells allows for second-to-second control of plasma calcium and helps adjust the secretion of PTH accordingly. PTH's effect on the bone stimulates rapid mobilization of calcium by increasing bone resorption, which ultimately results in a transfer of calcium from mineralized bone to the blood stream. (2) At the cellular level, PTH stimulates osteoclast proliferation/differentiation indirectly by binding to the plasma membrane of osteoblasts, leading to the increased expression of RANK-L and down-regulation of osteoprotegerin (OPG). The

binding of RANK-L to RANK (on osteoclasts) induces osteoclast-mediated bone resorption. PTH can also induce the secretion of macrophage colony stimulating factor (M-CSF) by osteoblasts, promoting the differentiation of macrophage lineage cells and osteoclastogenesis.(3) In addition to promoting calcium release from bone, PTH can act on the kidneys to modulate the levels of plasma calcium and phosphate. It enhances calcium reabsorption at the distal tubule, phosphate excretion at the proximal tubule, and induces renal hydroxylases to catalyze the formation of biologically active vitamin D. (1) PTH-related protein (PTHrP) is an agonist at the PTH receptor and has similar effects on plasma calcium when produced by certain tumors. Excess PTHrP may lead to hypercalcemia of malignancy, and is typically associated with lung and breast cancer. (4)

Vitamin D is also known as the "sunshine vitamin" because it can be synthesized in the skin when sun exposure is adequate. It is better classified as a steroid hormone as it is synthesized from cholesterol and carried in the blood stream, having diffuse effects throughout the body. (5) Vitamin D requires proper liver and kidney function in order to be converted to 1, 25-dihydroxyvitamin D (calcitriol), the biologically active form of Vitamin D. Vitamin D is activated by hydroxylation of positions 1 and 25 of the molecule in the liver and kidney; it is deactivated by hydroxylation of the 24 position by the CYP24A1 and CYP3A4 liver enzymes. The activity of these enzymes is governed by the levels of calcium, PTH, and calcitriol.

There are two forms of vitamin D that can be used for supplementation purposes, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Ergocalciferol is derived from plant sources while cholecalciferol is manufactured in the skin, and although they have structural differences, they can both be used to form active Vitamin D in the body. (2) Historically D2 and D3 were thought to be equally effective, however recent research suggests D3 is more stable and superior at raising plasma levels of calcitriol. (6) Calcitriol, the biologically active form of vitamin D, plays an important role in maintaining plasma levels of calcium and phosphate (Figure 1). Calcitriol can act in the GI tract to increase the production of calbindin, a transport protein that facilitates the movement of calcium into the bloodstream. Additionally, it can promote the expression of epithelial calcium channels in the GI lumen, further increasing calcium absorption. Calcitriol also exerts its effects in the kidney, promoting renal calcium absorption through calbindin. This hormone is also paramount for normal skeletal mineralization since it increases the availability of calcium and phosphate by virtue of its actions in the GI tract and kidney. Lastly, active vitamin D promotes osteoclastogenesis by inducing RANK-L and suppressing OPG expression, eventually leading to the deposition of calcium into the bloodstream. (1,2)

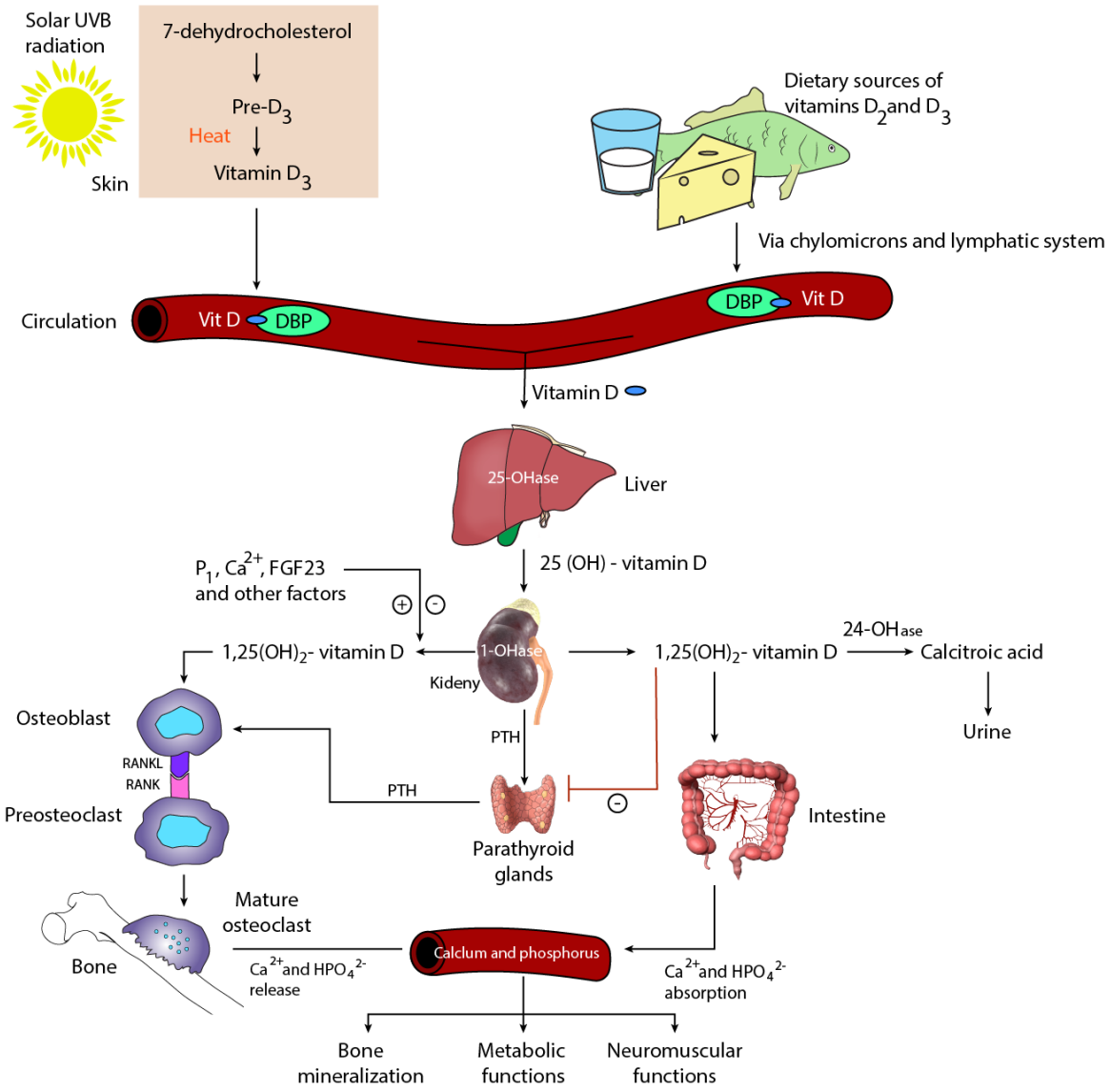

Figure 1. Synthesis and mechanism of action of vitamin D.

The role of vitamin D in selected disease states

Cardiovascular disease

The effect of vitamin D on hypertension and cardiovascular disease (CVD) has long been a topic of interest. Research in mice has found that vitamin D plays an inhibitory role in the renin-angiotensin system (RAS). (7) In vitro studies done by Talmor et al. have shown that calcitriol (active vitamin D) acts as a protective agent by reducing endothelial stress caused by advanced glycation end products, ultimately resulting in a decrease in inflammation and atherosclerotic parameters. (8) Studies have also shown that vitamin D is associated with a decrease in inflammatory markers and an increase in anti-inflammatory markers, both of which are

beneficial to preventing CVD.(9,10) Vitamin D has also been shown to be cardioprotective by decreasing vascular smooth muscle cell proliferation, inflammation and thrombosis. (11-13)

Another area of research interest has been Vitamin D's relationship with hypertension. Numerous studies have looked for a beneficial effect for hypertension including the Women's Health Initiative Trial, which was a long term national health study initiated by the NIH. This study examined heart disease, breast cancer, and osteoporosis in post-menopausal women and found no benefit with regard to hypertension in women taking 400 IU/day of Vitamin D plus 1000 mg/day of calcium. (14) Another study by Jorde et al. investigating vitamin D supplementation and weight loss showed that women taking 20,000 -40,000 IU vitamin D per week showed no significant difference in blood pressure at 1 year even though serum calcitriol levels increased significantly.(15) A recent large prospective study found that low 25-hydroxyvitamin D was associated with increased risk for developing hypertension; however, the same study found that high levels of 1,25-dihydroxyvitamin D was also associated with increased risk of developing hypertension. (16) The exact role of vitamin D in the cardiovascular system is still not completely clear, but large clinical trials have shown that vitamin D has no benefit in the treatment or prevention of hypertension. (14-17)

Fall prevention

Falls present a major health concern to the elderly population worldwide with one out of three older adults falling per year. (18) Falls not only result in serious injury, but the resulting emergency room visits generate great strain on the healthcare system. Studies have shown that vitamin D receptors located in human muscle may have a direct role in muscle strength. (19,20) Thus, it is no surprise that vitamin D deficiency can lead to severe myopathy, increasing the risk of falling. (21) A meta-analysis by Bischoff-Ferrari et al found that supplementation with 700-1000 IU/day or achieving 25(OH)D levels between 24-38 ng/ml reduced the risk of falling by 19%.(22) However, a 2015 randomized, placebo controlled trial indicated that high dose cholecalciferol (50,000 IU twice monthly) increases calcium absorption but does not have a beneficial effect on bone mineral density, muscle function, muscle mass, or falls.(23) It is becoming apparent that vitamin D and calcium must be supplemented together to provide beneficial effects for fall prevention.(24,25)

Cancer risk reduction

More than 275 epidemiological studies have been done looking at the association of Vitamin D and cancer risk reduction with the majority of these studies showing an overall decrease in cancer in patients with elevated serum 25(OH)D. (26) The Third National Health and Nutrition Examination Survey (NHANES III) showed that increased exposure to UVB radiation in women decreased the incidence of breast cancer by one-half compared to women with less sun exposure. (27) In the same survey, men with higher UVB exposure demonstrated a 50% reduction in prostate cancer.(26,28) In another study examining the association between colon cancer and 25(OH) D levels, the investigators found that higher 25(OH) D levels were associated with significant reductions in overall mortality. (29) Additionally, data from NHANES III shows that individuals with 25(OH)D levels > 32 ng/mL have one fourth the risk of dying from colon cancer. (30) A recent randomized controlled trial (RCT) performed by Lappe et al. showed that

vitamin D supplementation at 1100 IU/day in conjunction with calcium supplementation of 1450 mg/day led to a 60% reduction in incidence of all invasive cancers combined. (31) The National Academy of Science recommends an upper limit of intake for vitamin D at 2,000 IU/day. (32) According to data estimates by Garland et al., intake of 2,000 IU/day vitamin D would lead to a 25% reduction in the incidence of breast cancer and a 27% reduction in incidence of colorectal cancer in north America.(26) Studies have evaluated the biochemical effects of vitamin D on cancer prevention; the majority of these studies have concluded that vitamin D's mechanism is multifactorial, involving up-regulation of signaling and adherence between epithelial cells, cell to cell contact inhibition, cellular differentiation, stabilization of cell life cycle, promotion of automated cell death, and inhibition of angiogenesis among several others. (26)

Disease Consequences on Vitamin D Levels

There are many disease states that can alter the metabolism of vitamin D, calcium, and phosphate. In some instances, additional supplementation may be dangerous due to the intricate nature of calcium homeostasis and the role that vitamin D plays in it. No specific guidelines or literature currently exist regarding the adjustment of supplementation with specific disease states. However, the overall theme is generally the same: caution should be used in regards to nutrient supplementation in patients with diseases that are known to increase calcium levels.

Cancer

The most common cause of hypercalcemia in the inpatient population is cancer. Hypercalcemia is common (20-30%) in patients with both hematologic and solid tumor malignancies, particularly breast cancer, lung cancer, and multiple myeloma.(33) In cancer patients, there are three predominant mechanisms which contribute to hypercalcemia. These mechanisms include tumor secretion of parathyroid hormone-related protein (PTHrP), tumor production of 1,25-dihydroxyvitamin D, and osteolytic metastases with cytokine release. (33,34) Hodgkin lymphoma is an example of increased production of 1,25-dihydroxyvitamin D leading to hypercalcemia; this occurs in almost all cases. (35,36)

Cardiovascular and Chronic Kidney Disease

Patients with atherosclerosis should avoid excess vitamin D. Medial smooth muscle cells possess an enzyme system along with an intracellular receptor for vitamin D, suggesting that vasculature is an important target.(10) Research shows that excess vitamin D intake contributes to vascular calcification. (37) An in vitro bovine study found that 1,25-dihydroxyvitamin D may stimulate vascular calcification by blocking the expression of endogenous inhibitors such as PTHrP.(37) The same study also suggested that the stimulatory effects of vitamin D on osteopontin and alkaline phosphatase may also contribute to vascular calcification.(37) Another study demonstrated an association between coronary artery calcification and carotid intima-media thickening in children with high 1,25-dihydroxyvitamin D.(38,39)

Patients with chronic kidney disease, particularly those with end-stage disease on dialysis should be cautious about consuming excess vitamin D.(40) Cardiovascular disease is a leading cause of death in the dialysis patient population and may largely be due to excess vascular calcification, chiefly coronary artery calcification. Studies have shown that excessive vitamin D therapy can cause arterial calcification.(37,41,42) A postmortem investigation of children with end stage renal disease reported an association between vitamin D therapy and vascular calcification.(41) Also, a retrospective study of patients who received long term dialysis reported a relationship between levels of vitamin D metabolites and the extent of vascular calcification. (42)

Hyperparathyroidism

Primary hyperparathyroidism is a condition in which the parathyroid glands become overactive and secrete excessive amounts of parathyroid hormone. Hyperparathyroidism can be caused by an adenoma, hyperplasia, carcinoma, or chromosomal defects. Familial isolated hyperparathyroidism, not associated with any other condition can be part of another endocrine disorder such as multiple endocrine neoplasia (MEN) type 1 and 2A. Single adenomas account for the majority of primary hyperparathyroidism. Patients with any of these conditions lack proficient calcium level regulation due to overactive glands and ineffective negative feedback. Vitamin D insufficiency is common in patients with primary hyperparathyroidism, and in a study by Grey et al. in 2005, preliminary data suggested that repletion of vitamin D in patients that were vitamin D deficient may decrease levels of PTH and bone turnover without exacerbating hypercalcemia.(43)

Sarcoidosis

Sarcoidosis is a systemic inflammatory disease resulting in granulomas that most commonly appear in the lungs or lymph nodes. As with other granulomatous diseases, sarcoidosis has abnormal calcium metabolism. A large number of patients with sarcoidosis are hypercalcemic. Within the granulomas, activated macrophages convert calcidiol to calcitriol independently of the physiologic PTH-calcium regulatory system. (44-47) These activated macrophages differ from normal calcitriol producing macrophages in that they have no self-regulated negative feedback system.(48) Supplemental vitamin D intake could potentiate hypervitaminosis D, resulting in a variety of symptoms, from irritability and fatigue to a metallic taste and memory loss.

Other diseases with hypercalcemia

Familial hypocalciuric hypercalcemia, also known as familial benign hypercalcemia, is an autosomal dominant disorder that results from an inactivating mutation of the gene for the calcium-sensing receptor (CaSR). CaSR is located in many different tissues, most notably the parathyroid gland, kidneys, thyroid C-cells, intestine, G-cells in the stomach, osteoclasts and osteoblasts. Since this receptor is located on many calcium regulating organs, its mutation greatly impacts calcium homeostasis. This receptor detects changes in serum ionized calcium and responds by functioning differently in the parathyroid gland and kidney. For example, a mutated CaSR on the C-cell of the parathyroid inaccurately perceives low levels of calcium and

increases levels of PTH in an attempt to correct this perceived low calcium. With the increased possibility for errors in calcium balance, patients with familial hypocalciuric hypercalcemia should be cautious with supplemental vitamin D. (49,50)

A former classic cause of hypercalcemia, milk-alkali syndrome is resurging and is now the third leading cause of hypercalcemia. Milk-alkali syndrome is a constellation of hypercalcemia, metabolic alkalosis, and renal insufficiency caused by ingestion of large amounts of calcium along with an absorbable alkali such as calcium carbonate or milk and sodium bicarbonate. Three factors are responsible for this increase in incidence: the emphasis on calcium therapy for osteoporosis, the availability of non-prescription calcium carbonate preparations, and the use of calcium carbonate in chronic renal failure. For the majority of patients with milk-alkali syndrome, the symptoms are only transient because normal renal function and the suppression of calcitriol production allow maintenance of calcium and acid-base balance. Experimental studies investigating calcium carbonate ingestion and suppression of calcitriol levels showed that not all normal individuals would suppress calcitriol to the same extent. (51,52)

As outlined above, vitamin D and calcium have intricate regulatory systems in the body and interact with the gastrointestinal, endocrine, musculoskeletal, and neurological systems. While vitamin D is without question an important nutrient, patient's receiving supplementation should be closely monitored for hypercalcemia and/or sequelae of hypercalcemia if they have any of the comorbid conditions listed above.

Vitamin D Drug Interactions

Vitamin D is known to interact with numerous drug classes. Some drugs such as anticonvulsants lower the activity of vitamin D in the body, while other interactions, such as with bile acid sequestrants, decrease vitamin D absorption. A recent review by Gröber et al. (2012) discussed drug interactions with vitamin D through the pregnane X receptor (PXR). (53) A summary of these findings as well as other potential interactions not related to PXR is provided below.

Pregnane X Receptor Interactions

PXR is an intracellular receptor that shares 60% homology with DNA binding domains of the vitamin D receptor; therefore, it has the ability to bind and activate DNA response elements that upregulate the 24-hydroxylase enzymes deactivate vitamin D. Ligands for the PXR are diverse and include numerous commonly used drug classes: antihypertensives, antiepileptics, antineoplastics, antibiotics, anti-inflammatories, antiretrovirals, endocrine drugs, and some herbal medications.(53-56) The induction of these hydroxylase enzymes lowers vitamin D levels, and may be responsible for the osteomalacia associated with antiepileptic usage. (57-60) Patients using the classes of drugs listed above should be monitored closely for vitamin D status and adequate supplementation should be provided, keeping in mind that higher than normal dosages of vitamin D may be required.

Other P450 Enzyme Interactions

Theophylline, a bronchodilator with anti-inflammatory properties, has been used in the treatment of COPD and asthma for over 75 years. However, its use has declined markedly due to its narrow therapeutic index and numerous drug interactions.(61) Elimination occurs via the CYP450 system, primarily by the CYP1A2 and CYP2E1 isozymes. These enzymes are also responsible for metabolizing numerous other agents such as macrolide and quinolone antibiotics, oral contraceptives, benzodiazepines, and certain antidepressants. Aside from being a substrate of CYP450 enzymes, theophylline induces certain isozymes responsible for the elimination of vitamin D. A study performed by Fortenbery et al. showed that rats given theophylline had decreased levels of circulating vitamin D, increased calcium excretion, and decreased plasma calcium levels. (62)

Isoniazid (INH) and rifampin are two agents commonly used in tuberculosis treatment. INH inhibits cell wall and DNA synthesis, while rifampin inhibits RNA polymerase. Studies performed by Brodie et al. demonstrated a significant decrease in both active and circulating levels of vitamin D in patients undergoing INH/rifampin treatment. (63,64) Additionally, the findings of Wang et al. show that rifampin can induce the CYP3A4 pathway and speed up the metabolism of vitamin D.(65) It is known that patients with tuberculosis are already at risk for altered calcium homeostasis, thus utilizing these agents should warrant close monitoring of calcium, PTH, and vitamin D levels.

Patients with epilepsy often express concern about potential side effects from chronic therapy with antiepileptic medications, especially medications that interact with the cytochrome P450 (CYP450) system. Phenytoin has been shown to promote breakdown of 25-hydroxyvitamin D (25-OHD) to less biologically active analogs with subsequent development of clinically significant osteomalacia.(66) More recently, carbamazepine (CBZ) and its active metabolite, oxcarbazepine (OXC) have raised concerns for drug-induced osteomalacia because of their potent inducing effect on CYP450. Mintzer and colleagues conducted a placebo-controlled cross-over study and confirmed that patients treated with CBZ or OXC for six weeks experienced significant reduction in 25-OHD compared with placebo and developed changes in bone biomarkers suggestive of secondary hyperparathyroidism.(66) The authors concluded that the changes noted would be expected to produce clinically meaningful bone loss over time; they recommended that vitamin D supplementation be administered to patients receiving long-term treatment with CBZ or OXC.(66)

H2-receptor antagonists (H2RA) are commonly used in the treatment of gastroesophageal reflux disease (GERD). Most of these agents are at least partially metabolized through the CYP450 system, potentially interacting with several classes of drugs. Due to their CYP450 metabolism, H2RAs may decrease the conversion of vitamin D to its biologically active form, leading to a relative deficiency.(67,68) Odes et al. investigated the effects of cimetidine on hepatic vitamin D metabolism and found an increase in vitamin D levels upon withdrawal of cimetidine. (68) These results suggest patients on long-term therapy with cimetidine, or other H2-receptor antagonists should be monitored for vitamin D deficiency and provided supplementation when appropriate.

Drugs that alter the absorption of vitamin D

Cholestyramine is a bile acid sequestrant (BAS) used to treat hypercholesterolemia. It works by forming a non-absorbable complex with bile salts in the small intestine, increasing fecal loss of any LDL cholesterol that is bound to the salts. Fat soluble vitamins like vitamin D require bile salts for absorption, thus the use of cholestyramine (or other BAS) leads to decreased absorption of vitamin D and other fat soluble compounds. (69,70) Patients taking cholestyramine should be instructed to take vitamin D at least one hour before or four to six hours after their cholestyramine dose.

Mineral oil is commonly used for bowel irrigation and for the treatment of constipation. It is classified as a lubricant laxative and works by inhibiting colonic absorption of water leading to a decrease in stool transit time. (71) Vitamin D, being a fat soluble vitamin, is easily solubilized in the oil and thus is retained in the GI tract, decreasing its absorption. Patients taking vitamin D supplements should be advised to avoid taking vitamin D for several hours surrounding the ingestion of mineral oil.

Orlistat is a lipase inhibitor used to assist weight loss by decreasing fat digestion/absorption in the small intestine. This is beneficial in terms of weight loss; however, it can decrease absorption of fat soluble compounds like vitamin D. (72) Patients using orlistat should be monitored for vitamin D deficiency.

Heparin induced osteopenia

Unfractionated heparin (UFH) is a heterogeneous mixture of glycosaminoglycans that has been used clinically for over 50 years as an anticoagulant. It works by potentiating the effects of antithrombin, which inhibits the activity of clotting factors, namely thrombin and factor Xa. (71) While short term therapy with UFH has not been shown to significantly affect overall bone density, the use of UFH for long term thromboembolism prophylaxis is associated with decreases in both bone mineral density and calcitriol levels.(73-77) Low molecular weight heparins (LMWH) are fragments of UFH with a somewhat greater propensity for Xa inhibition and lower thrombin inhibition than UFH. Initial research indicated that LMWHs had less effect on bone metabolism, however one study revealed no difference between the two preparations.(78-80) The action these drugs have on lowering bone mineral density is not well understood, but histomorphometric evidence points to both increased bone resorption and decreased mineral deposition.(74,81) Studies examining calcitriol levels (1, 25-dihydroxyvitamin D) in women while on long-term heparin therapy revealed these women had significantly lower levels than women not taking heparin, indicating heparin may somehow inhibit the activity of 1α-hydroxylase in the kidney.(81-83) Because of this effect on bone mineralization and resorption, patients using heparin products may need increased dosages of vitamin D supplements.

Drug Induced Hypercalcemic States

As discussed above, disease states of hypercalcemia warrant extra caution in regards to prescription or over the counter vitamin D preparations. This includes milk-alkali syndrome, a secondary cause of hyperparathyroidism from the repeated ingestion of calcium carbonate. In

addition to disease, hypercalcemia is associated with several commonly used drugs such as lithium, theophylline (discussed above) thiazide diuretics, and tamoxifen.

Bipolar disorder is a psychiatric illness associated with both major depressive episodes mixed with either manic or hypomanic episodes. Although newer treatments for bipolar disorder exist, lithium remains one of the first line agents for treatment. Thyroid dysfunction is one of the most well-known side effects of long term lithium use; however, one of the less well known, yet potentially life threatening side effects of lithium therapy is primary hyperparathyroidism and its associated hypercalcemia.(84,85) Different mechanisms for causing hypercalcemia and hyperparathyroidism have been proposed, although there is inconclusive evidence as to which is correct.(84,86) One study proposes that lithium may raise the threshold of calcium-sensing mechanisms. (86) Another study shows that lithium can competitively inhibit calcium transport across cell membranes, leading to increased blood calcium levels. (84) Regardless of which theory is correct, plasma calcium should be measured at baseline prior to starting lithium and should be rechecked periodically throughout treatment. (85) Additional care and attention should be given to patients also taking vitamin D supplements due to the increased risk for hypercalcemia.

For years, the interaction between thiazide diuretics, PTH, and vitamin D has been exploited clinically for the treatment of renal stones and familial hypercalciuria. Thiazides consistently produce a drop in urinary calcium excretion, an effect attributed to enhanced reabsorption of sodium and calcium at the proximal convoluted tubule in response to sodium depletion. In contrast, the effect of thiazides on plasma calcium concentration is more complex. Thiazide diuretics do not routinely raise plasma calcium concentration; however, in certain patients, especially those with elevated PTH, thiazide diuretics may produce a clinically significant rise in serum calcium concentration. Studies by Parfit show that the effects of thiazides on serum calcium may be summarized as follows: first, in the presence of hyperparathyroid hormone, thiazide diuretics increase calcium reabsorption in the kidney and release from bone; second, in the presence of normal amounts of PTH and vitamin D, thiazide diuretics increase calcium reabsorption in the kidney but do not increase calcium release from bone; third, in the presence of reduced or no PTH but an excessive amount of vitamin D, thiazide diuretics do not alter calcium reabsorption but do increase calcium release from bone; and fourth, in the absence of both PTH and vitamin D, thiazide diuretics do not alter calcium reabsorption or calcium release from bone.(87) In summary, PTH regulates the action of thiazide diurectics on renal calcium handling, whereas vitamin D regulates the action of thiazides on bone calcium release. (87)

Selective estrogen receptor modulators (SERMS) are agents that act on the estrogen receptor with tissue dependent agonist and antagonist activity. Tamoxifen, a first generation SERM, is antiestrogenic in breast cancer cells, and is used clinically for the treatment of estrogen-receptor positive breast cancer. It has been in use for over 30 years and has a well-defined safety and efficacy profile. (71) Although it has proven invaluable as an adjunctive treatment, it may possess deleterious side effects including endometrial cancer, increased risk of stroke, and hypercalcemia. Of particular note is hypercalcemia, which is well documented in the literature and is potentially life threatening. (88,89) The incidence of tamoxifen-induced hypercalcemia is between 5-10% and typically occurs during the first few weeks of treatment. (90) The hypercalcemia can be managed with immediate discontinuation of tamoxifen and prompt

treatment with anti-hypercalcemic drugs, however it is paramount to examine the patient's medication profile for any agents known to increase serum calcium, as they can potentially worsen the problem. (89,91)

Aluminum Toxicity

Acid indigestion (heartburn) affects a large portion of the US population, and it is estimated that 25-35% of Americans can be classified clinically as suffering from GERD. (92) Antacids are commonly used over the counter agents useful for treating symptoms of gastroesophageal reflux, as they have a rapid onset of action and are generally safe with few side effects. However, aluminum hydroxide, the active ingredient in some antacids, has the potential to interact with vitamin D. Aluminum absorption typically occurs passively in the small bowel; however, research has shown that certain compounds, namely vitamin D, can increase intestinal absorption leading to toxicity. (93,94) Aluminum toxicity is rare and is usually seen in patients with some degree of renal failure. Typically these patients are on hemodialysis; however, if patients present with signs/symptoms of aluminum toxicity, they should be queried about the recent use of both aluminum hydroxide and vitamin D supplements. Symptoms of aluminum toxicity are often nonspecific and include proximal muscle weakness, bone pain, nonhealing fractures, and altered mental status. Due to the potential for toxicity, it is generally recommended to take vitamin D either 2 hours before or 4 hours after aluminum hydroxide formulations.

Synergistic drug interactions

Doxorubicin is an anthracene derivative commonly used in the treatment of breast cancer, acute lymphoblastic leukemia, and small cell lung cancer. It exerts effects by inhibiting the action of topoisomerase II, an enzyme necessary for DNA replication. This agent can also increase production of free radicals, causing oxidative damage and cell death. Vitamin D3 has been shown to enhance the effects of doxorubicin on cancer cells through the potentiation of free radical cytotoxicity. A possible explanation for this phenomenon lies in the finding that vitamin D treated cells showed diminished activity of superoxide dismutase, a key scavenger of free radicals. (95)

Digoxin is an inotropic agent used it in the treatment of heart failure. The mechanism of digoxin's inotropic effects is through the inhibition of the sodium/potassium ATPase in myocardial muscle cells. This causes increased intracellular sodium, which promotes calcium influx via a sodium-calcium antiporter. The resultant rise in intracellular calcium increases the contractility of the myocardial cells. Hypercalcemia is thought to increase the propensity for digoxin toxicity by shortening the refractory period in ventricular cardiac muscle cells. (96) Since high levels of vitamin D are known to cause hypercalcemia, patients taking digoxin and vitamin D concurrently should be closely monitored for digoxin toxicity. There are even reports of hypercalcemia induced digoxin toxicity occurring with normal serum digoxin levels. (96-98)

Table 1. Potential drug interactions that result in lower levels of active vitamin D. Interactions with these drugs may necessitate higher-than-normal levels of vitamin supplementation to achieve adequate results.

Mechanism	Drugs / Drug Class(es)	Interaction Result
Pregnane X Receptor activation	Antihypertensives Antiepileptics Antineoplastic drugs Antibiotics Anti-inflammatories Antiretrovirals Endocrine drugs Herbal medications	Increased rate of vitamin D inactivation
P450 Enzyme Induction	CYP1A2 and CYP3A4 inducers (Theophylline, Isoniazid, Rifampin)	Increased metabolism of vitamin D to inactive form
P450 Enzyme Inhibition	Cimetidine	Decreased conversion of vitamin D to active form
Decreased gut absorption	Bile acid sequestrants (Cholestyramine) Mineral Oil Orlistat Olestra	Decreased absorption of vitamin D due to decreased absorption of all fat soluble vitamins
Inhibited activity of 1α-hydroxylase	Heparin Low molecular weight heparins	Lower levels of active vitamin D

Table 2. Drug interactions that may result in a build-up of potentially dangerous substances leading to adverse effects. Patients taking these substances should be carefully monitored for their vitamin D and calcium status. Supplementation should be used cautiously.

Mechanism	Drugs / Drug Class(es)	Interaction Result
Hyperparathyroidism	Lithium	High calcium levels that could be potentiated with excessive vitamin D supplementation
Hypercalcemia	Calcium containing substances	Milk-alkali syndrome may result if predisposed to hypercalcemia while taking excessive vitamin D supplements
	Tamoxifen (SERMs)	Tamoxifen may cause life threatening hypercalcemia in breast cancer patients
Aluminum absorption	Aluminum-containing antacids	Aluminum toxicity due to excessive absorption of aluminum through gut wall related to vitamin D

		absorption in the gut

Table 3. Synergistic drug interactions. Vitamin D can be used to enhance the effects of these drugs.

Drug	Interaction and Result
Doxorubicin	Vitamin D decreases activity of superoxide dismutase thereby enhancing the oxidative effect doxorubicin has on cells
Digoxin	Hypercalcemia resulting from excessive vitamin D intake shortens the refractory period of cardiac cells which increases the potential toxicity of digoxin, even at therapeutic levels

Conclusion

Vitamin D deficiency is widespread in the US population. (6) Supplementation of this vitamin is becoming more common in our society, as research has shown the molecule to play a critical role in numerous physiological processes as well as a potential role in multiple disease processes including cancer, cardiovascular disease, and fall risk. However, as we have discussed, numerous disease states can affect calcium homeostasis, so it is essential for prescribing physicians to fully understand the vitamin D-calcium relationship with regard to these diseases. Additionally, several potential drug interactions exist for vitamin D, which can affect the amount of vitamin D that must be taken to achieve adequate levels.

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