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Answers About the Need for Vitamin D Supplementation

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Abstract
Vitamin D has a significant role in bone health, calcium homeostasis, immune function and other biological functions. In our bodies, the main source of vitamin D is linked to our skin's exposure to sunlight. It can also be obtained through foods that contain vitamin D. Despite these two sources, vitamin D supplementation is often necessary. It is available in two forms, cholecalciferol and ergocalciferol as over-the-counter (OTC) products, as well as calcitriol as prescription only. Reasons for vitamin D deficiency include lack of sunlight, poor diet, malabsorption of vitamin D, liver and/or kidney disease. Vitamin D deficiencies lead to diseases such as rickets, osteomalacia and osteoporosis. During supplementation it is important to monitor for vitamin D toxicity. Pharmacists need to be aware of the various guidelines regarding vitamin D supplementation.

Introduction

Vitamin D, a fat-soluble vitamin, is important for overall health and well being in both adults and children. In recent years, vitamin D deficiency has been "over-hyped," and claims that supplementation can 'cure' various disease states have been unsubstantiated. Recommended daily doses also continue to vary between different governing bodies, including the National Osteoporosis Foundation (NOF) and the Institute of Medicine (IOM). Additional inconsistency exists in the literature concerning normal plasma vitamin D levels which then defines vitamin D deficiency. Due to vitamin D's significant role in bone health, calcium homeostasis, immune function, and other biological functions, many foods in the United States are fortified with vitamin D.[1]

How We Get Vitamin D

The main source of vitamin D in our bodies is derived from our skin secondary to sunlight exposure. Skin uses ultraviolet (UV)-B rays (290 nm - 315 nm) to convert 7-dehydrocholesterol to cholecalciferol, which is also referred to as vitamin D_3. Cholecalciferol is transported to the liver via a vitamin D binding protein where it is converted by the enzyme 25-hydroxylase to calcifidiol which is also referred to as 25-hydroxycholecalciferol abbreviated 25(OH)D, calcifidiol or *calcidiol*.[2] Calcifidiol is then transported to the kidney where it is converted to calcitriol by the enzyme 1-alpha hydroxylase. Calcitriol, which is also referred to as 1,25-dihydroxycholecalciferol (abbreviated 1,25(OH)2D), is the most biologically active form of vitamin D. It is utilized to carry out various physiological functions, namely aiding our body in the absorption of calcium.[2] As previously stated, vitamin D is synthesized by the body in response to sunlight exposure, therefore any increased pigmentation will act as a natural sunscreen and ultimately reduce the amount of vitamin D that is produced from UV-B exposure. Vitamin D can also be obtained naturally from food sources such as oily fish like cod, mackerel, salmon and sardines while milk, cereal, yogurt and orange juice are fortified with vitamin D.[3]

Vitamin D Products

Although vitamin D is found in many foods and is readily activated in the skin by the sun, supplementation may be necessary to maintain an overall healthy state. Over-the-counter (OTC) sources of vitamin D contain either the compound cholecalciferol or ergocalciferol, which are commonly referred to as vitamin D_3 and vitamin D_2 respectively.[4] Ergocalciferol (vitamin D_2) is a plant-derived source, while supplemental cholecalciferol (vitamin D_3) is a synthetic form similar to what the body synthesizes in the skin via UV exposure.[5] It is important to note that cholecalciferol and ergocalciferol have both OTC and prescription products as outlined in Table 1.[4] Calcitriol, the active form of vitamin D, is only available by prescription.[5] Calcitriol is reserved for individuals with idiopathic and postsurgical hypoparathyroidism, pseudohypoparathyroidism and secondary hyperparathyroidism in those with moderate to severe chronic renal failure not yet on dialysis, and also those undergoing chronic renal dialysis. These individuals cannot convert calcifidiol to calcitriol in adequate amounts to maintain physiologic levels of plasma calcium. More information on specific dosage forms and doses are outlined in Table 1.

Vitamin D Deficiency

Common causes of vitamin D deficiency include lack of exposure to sunlight, poor diet and/or malabsorption of vitamin D. Medications such as phenobarbital, phenytoin, orlistat and corticosteroids can also lead to vitamin D deficiency. Phenobarbital decreases hepatic metabolism of vitamin D, specifically impacting the cytochromes responsible for the activity of vitamin D-25 hydroxylases that convert cholecalciferol to calcifidiol.[6] Phenytoin also induces activity of the cytochrome P450s in the liver and may additionally affect bone formation and resorption, calcium absorption and response of osteoblasts to parathyroid hormone.[7] Orlistat, brand name Alli®, was found to decrease the levels of 25-OH vitamin D even with the subjects taking multivitamins containing 400 IU of ergocalciferol.[8] Orlistat works by decreasing absorption of dietary fats, thus absorption of vitamin D, a fat-soluble vitamin, would also be expected to be negatively impacted.[9] Malabsorption conditions such as inflammatory bowel disease (IBD), cystic fibrosis (CF) and celiac disease may affect vitamin D absorption as well.

Additional causes of vitamin D deficiency include both liver and chronic kidney disease, as both organs are needed to convert vitamin D to its active metabolite. Plasma levels of calcifidiol (25-hydroxycholecalciferol or (25-OH)D) are measured to determine nutritional deficiency of vitamin D and/or lack of sunlight exposure. Plasma levels of calcitriol

Table 1. Vitamin D Products Including Dosage Form and Dose.[4]

		Capsule	Tablet	Liquid	Other
OTC Products	**Cholecalciferol**				
	Vitamin D_3 Super Strength	1,000-50,000 units	400-5,000 units & 50,000 units	400 units/mL & 2,000 units/0.3 mL & 5,000 units/mL	
	Ergocalciferol				
	Vitamin D_2		400 units & 2,000	8,000units/mL	
Rx Products	**Cholecalciferol**				
	Vitamin D_3 Super Strength	25,000 units (Decara)			
	Ergocalciferol				
	Vitamin D_2	50,000 units			
	Calcitriol				
		0.25 mcg & 0.5 mcg		1 mcg/g	Ointment 3 mcg/g
					IV Solution 1 mcg/g

(1,25-dihydroxycholecalciferol or 1,25(OH)2D are used clinically to confirm diagnosis of vitamin D deficiency rickets, parathyroid disorders and deficiencies in renal function.[10] Plasma vitamin D levels are not used diagnostically or to define a nutritional deficiency because this level will only provide data on recent sunlight exposure.[11]

Disease of Vitamin D Deficiency

Vitamin D deficiencies contribute to the development of diseases such as rickets, osteomalacia and osteoporosis. These conditions are characterized by weak bones, deficient vitamin D levels and, possibly, consequential hypocalcemia. All three impair the process of bone mineralization which relies on vitamin D to increase plasma calcium levels via increased intestinal absorption and decreased renal excretion. However, they differ in regard to the locations that are impacted. Osteomalacia occurs in regular bone, whereas rickets occurs specifically at growth plates and thus is a disease that can only affect growing children. Osteomalacia is often challenging to diagnose, but can be identified by bone pain, specifically in axial bones such as the legs and a 'waddling' gait.[12] Treatment of osteomalacia is very basic, focusing on relieving the pain and preventing fractures. Treatment consists of supplementation with vitamin D, calcium and possibly phosphate. When possible, the cause should be determined and rectified.[12]

As mentioned, rickets is characterized by issues at growth plates, which sets it apart from osteomalacia. Depending on the age of the pediatric patient, the manifestation of rickets can vary.[12] Neonatal growth occurs most rapidly in the skull, so rickets will manifest in skull formation in that subpopulation. In children 1 year of age, rickets will manifest in the wrists and rib cage, while inward or outward bowing of the legs is seen in toddlers.[12] The type of rickets (primary versus secondary) is defined by the cause of vitamin D deficiency. Primary or nutritional vitamin D deficiency is caused by either inadequate diet or inadequate exposure to sunlight.[12] This diagnosis is confirmed with testing for 25-OH vitamin D levels in the blood. If the level is low, treatment with calciferol is initiated.[12] Secondary vitamin D deficiency is caused by another disease state (such as gastrointestinal disease, pancreatic diseases, hepatic diseases, celiac disease or primary biliary cirrhosis) that impacts absorption of vitamin D.[12] Treatment is the same as primary vitamin D deficiency: calciferol supplementation. Calcium deficiency, also known as calciopenic rickets, can exacerbate vitamin D deficiency rickets. Adding calcium, either through diet or supplementation, will correct calciopenic rickets. Metabolic acidosis can also cause rickets, but this condition is easily treated with vitamin D supplementation and alkali therapy.[12] Certain genes can also contribute to rickets. X-linked hypophosphatemia (XLH) is a hereditary condition in which the patient's ability to convert vitamin D to its active form is

changed. The XLH patients will present with a short stature and bowed limbs but not the fractures or muscle weakness associated with other forms of rickets.[12] Standard treatment is calcitriol, the activated form of vitamin D, and phosphate tablets.[12] With XLH, activated vitamin D is given because the patient is not able to convert the inactive forms into the usable active forms. Other genetic defects can cause issues in either the synthesis of vitamin D or produce resistance in the tissues to vitamin D.[12]

Osteoporosis is another disease related to vitamin D deficiency. With osteoporosis, bone is either not being formed, mineralized or is breaking down.[13] A patient with osteoporosis has a loss of bone density, which predisposes them to fractures. Physical symptoms of osteoporosis include loss of height over time or a stooped back due to weak vertebrae that can collapse or break easily.[14] Osteoporosis affects 52 million Americans and costs approximately $19 billion a year.[14] Osteoporosis is linked with deficiencies in calcium, hormones such as estrogen and vitamin D.[15] Vitamin D has a role in the pathophysiology of osteoporosis due to its involvement in calcium homeostasis. Calcium is a necessary mineral required for bone formation and maintenance, and it cannot be absorbed from the gastrointestinal tract without vitamin D.[15,16] Specifically, vitamin D stimulates the synthesis of calbindin, a transport protein for calcium. This protein moves calcium from the apical side of mucosal cells of the gastrointestinal tract (GIT) to the basolateral side, which is in contact with systemic circulation.[16] Because of its role in the absorption of calcium, supplementation of both vitamin D and calcium is recommended for osteoporosis patients.[17] In the Decalyos II study, investigators found that, compared to placebo, both those taking a combination tablet (1200 mg calcium and 800 IU vitamin D) and the two ingredients simultaneously in two separate tablets experienced significantly improved vitamin D levels and lower parathyroid hormone (PTH) levels when compared to placebo.[18] Parathyroid hormone is released when plasma calcium levels are low. Parathyroid hormone stimulates vitamin D activation and calcium resorption from the bone, and a lowering of PTH is indicative of increasing calcium levels.[19] The 389 subjects taking both vitamin D and calcium had an unchanged bone density test after 12 months while the placebo group (n=194) saw a decrease in bone density in both the femur and the radius, but the change was not found to be statistically significant (p=0.09, p=0.48 respectively). This double-blinded study supports supplementing with both vitamin D and calcium in patients diagnosed with osteoporosis to prevent disease progression.[18]

Influence of Malabsorption Disorders on Vitamin D

Kuwabra et al., using a value of less than 15.7 ng/ml as their definition of vitamin D deficiency, investigated the incidence of vitamin D deficiency in those with IBD, Crohn's disease and ulcerative colitis. They reported that subjects with IBD were, on average, deficient in vitamin D. Subjects with Crohn's disease had even lower 25(OH)D levels (11.2ng/mL), while subjects with ulcerative colitis had an average 25(OH) D level (20.2 ng/mL).[20] Crohn's disease involves more of the upper GIT compared to ulcerative colitis, and thus damage in the upper GIT would more dramatically impact absorption of vitamin D. Jahnsen et al. compared 25(OH)D in 60 patients with Crohn's disease and 60 patients with ulcerative colitis. They found that patients with Crohn's disease had lower concentration of 25(OH)D on average, though the difference was not statistically significant. The lower levels of vitamin D were attributed to malabsorption of the vitamin from the GIT, and the researchers concluded that supplementation with vitamin D should be considered for patients with Crohn's disease.[21] Celiac disease can also interfere with the absorption of vitamin D.[22]

Cystic fibrosis is known to interfere with absorption of fat-soluble vitamins, so it would interfere with the absorption of vitamin D as well. Lark et al. compared patients with cystic fibrosis to a control group (those without CF) and found that vitamin D absorption is lower in patients with CF than in the control group. Although the CF subjects were taking pancreatic enzymes to help with the intestinal absorption of the vitamin D supplementation, their 25(OH)D levels were still lower than the control group (p=0.0012). This suggests that not only is absorption of vitamin D an issue in CF, but CF may also alter some other pathway in its metabolism.[23] One proposed mechanism is an increased clearance of 25(OH)D through increased activity of cytochrome P450 enzymes. Activity of cytochrome P450 enzymes is increased in patients with CF, which could increase the metabolism and clearance of vitamin D in the body. [23,24]

Interference with vitamin D synthesis to an active form can also lead to deficiency. As both the liver and kidneys are needed for calcitriol synthesis, impairment of either hepatic or renal function can result in vitamin D deficiency. Arteh et al. examined 118 patients with chronic liver disease and found that 92.6 percent were deficient in vitamin D, which was defined as serum 25(OH)D levels of less than 32 ng/mL. When the subjects were further broken down into various populations, females had a significantly higher risk of being vitamin D deficient than males, and African Americans had a significantly higher risk of being vitamin D deficient than Caucasians.[25] Chronic kidney disease will also interfere with vitamin D levels. Bansal et al. reported average serum 25 (OH)D levels of 10.14 ng/mL in 45 subjects on hemodialysis. Of the subjects investigated, 88.9 percent were concluded to be vitamin D deficient despite supplementation with 400 to 600 IU of cholecalciferol.[26] Holick proposed that the deficiency in active vitamin D in patients with kidney disease is associated with hyperphosphatemia which inhibits production of 1,25(OH)2D, the final, biologically active form of vitamin D produced by the kidneys. Also, the low glomerular filtration rate of patients with kidney disease decreases production of the enzyme 1-alpha-hydroxylase, which is necessary to convert vitamin D to its active form.[27]

Individuals with the conditions mentioned above might want to consider not only vitamin D supplementation but also supplementing with the most appropriate form of vitamin D for their needs. In those who have a problem absorbing vitamin D from the intestine (celiac disease, IBD, nutritional rickets), supplementation with cholecalciferol (vitamin D_3) is pre-

ferred. In a study by Armas et al., it was concluded that cholecalciferol is present in the serum longer than ergocalciferol, and thus is the preferable type of vitamin D to use.[28] Cost and insurance coverage may also be an important consideration when choosing between ergocalciferol or cholecalciferol.

The active form of vitamin D, calcitriol, is available as Rocaltrol®. It does not require further conversion. Calcitriol is indicated in patients with chronic renal dialysis, for secondary hyperparathyroidism in patients with kidney disease and for low calcium in patients with parathyroid gland disorders.[29]

Vitamin D Toxicity

Use of vitamin D supplements and calcitriol may lead to vitamin D toxicity and it is important to educate on the potential harmful effects of hypervitaminosis D. Despite the common belief that more is better, there is no proven benefit for excessive intake of vitamin D, and it can potentially have negative effects with overdose.[31] Symptoms of vitamin D intoxication (VDI) range from increased calcium levels and formation of kidney stones to hardening of soft-tissue.[30-32] In 2010, the IOM also defined the vitamin D Upper Limit (UL), which is the maximum amount of vitamin D that can be ingested before experiencing harmful effects [33] These values can be found in Table 2 as well as comparisons made by NOF.

A retrospective study by Doneray et al. reported on the symptoms of VDI in infants prescribed vitamin D supplementation. In a majority of the patients, the vitamin D supplement was prescribed because patients were not reaching certain developmental markers, including walking, sitting and development of teeth, which is prevalent in rickets.[30] The symptoms that were noted included vomiting, constipation, weight loss, dehydration and hypercalcemia. Some patients even exhibited hypercalciuria and nephrocalcinosis, which are more serious conditions.[30]

Pharmacy Impact

Pharmacists need to be aware of the various guidelines regarding vitamin D supplementation (see additional resources listing at end of article). Individuals may become confused and overwhelmed with the different recommendations and choices of supplementations, causing them to seek the help of a pharmacist for advice on a daily dose specific to their needs. Table 2 lists the current recommendations of the IOM.

Pharmacists need to be aware that these organizations have different recommendations so that they can properly counsel patients coming in with questions. Pharmacists should also understand that vitamin D undergoes several hydroxylations in the body via the liver and kidneys. Therefore, a patient needing supplementation must have adequate kidney and liver function to activate the drug. If unable, a prescription form of vitamin D may be required. Pharmacists play a critical role in the expertise of OTC drugs, and vitamin D is one of these medications. With adequate education, pharmacists can make knowledgeable recommendations to patients to better their overall health.

Additional Helpful Resources

* http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/DRI-Values.aspx
* http://www.nlm.nih.gov/medlineplus/magazine/issues/winter11/articles/winter11pg12.html
* http://nof.org/articles/10

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Table 2. IOM Recommended Daily Allowances (RDA) and Upper Limits (UL) for Vitamin D.[33]

IOM (2010) Vitamin D		
Age	**RDA**	**UL**
Infant (0-6 months)	400 IU/day	1,000 IU/day
Infant (6-12 months)	400 IU/day	1,500 IU/day
Pediatric (1-3 years)	600 IU/day	2,500 IU/day
Pediatric (4-8 years)	600 IU/day	3,000 IU/day
Adolescent & Adult (9-70 years)	600 IU/day	4,000 IU/day
Adults (71+ years)	800 IU/day	4,000 IU/day

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