

CLINICAL PRACTICE

The emerging role of Vitamin D in asthma management

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Abstract

Purpose: Vitamin D deficiency and asthma share risk factors. Epidemiologists suggest that the U.S. prevalence of Vitamin D deficiency has increased as a result of the Westernization of culture and less time spent outdoors. Numerous studies support a patient's Vitamin D deficiency as a contributing cause to increased asthma symptoms, lower lung function levels, increased airway reactivity, and worsening asthma control. The purpose of the review article is to discuss the emerging role of Vitamin D in asthma management.

Data sources: A review of original research identified through MEDLINE and CINAHL and published in English was performed.

Conclusions: Research suggests promising benefits of Vitamin D supplementation in asthma patients with low (<30 ng/mL) Vitamin D levels. Evidence supports several possible mechanisms, including downregulation of allergen sensitivity and enhanced steroid responsiveness. Studies demonstrate that Vitamin D modifies airway hyperresponsiveness by minimizing airway inflammation. Ongoing studies seek to further evaluate the effects of Vitamin D supplementation on asthma and asthma morbidity.

Implications for practice: While there is no consensus on the use of Vitamin D as a mainstay in asthma treatment, research supports its consideration for use in asthma patients with low Vitamin D levels. Current evidence reinforces the need to measure Vitamin D levels for all asthma patients.

The emerging role of Vitamin D and its relationship to our health is a topic of growing interest to healthcare providers and patients. It is increasingly common to read well-designed studies on Vitamin D in an array of medical journals. According to published data from the Third National Health and Nutrition Survey, as reported in the Archives of Internal Medicine, 77% of Americans have low Vitamin D levels (Ginde, Mausbach, & Camargo, 2009). Researchers refer to the current state of Vitamin D deficiency in the United States as an epidemic (Ali, Arguelles, Langman, & Price, 2009). Epidemiologists suggest that the U.S. prevalence of Vitamin D deficiency has increased as a result of less time spent outdoors and dietary factors (Paul et al., 2012). Many diagnostic areas within health care have discovered that Vitamin D deficiency is linked to poor health outcomes. As it relates to asthma, numerous studies support Vitamin D deficiency as a contributing cause to increased asthma symptoms, lower lung function levels, increased airway reactivity, and worsening asthma control (Litonjua & Weiss, 2007). This article will present an evidence-based review of

Vitamin D's role in the management of asthma and discuss its clinical application for nurse practitioners (NPs).

Vitamin D's role in asthma

Zittermann, Gummert, and Börgermann (2009) found that individuals with low levels of Vitamin D have increased risk for asthma mortality. Vitamin D has an immunomodulator role from which all of its asthma-related benefits come from (see Figure 1; Benson, Toh, Vernon, & Jariwala, 2011). Vitamin D shifts the immune system's balance toward being less allergic, that is shifting the TH1 (type 1 T-helper cell)–TH2 (type 2 T-helper cell) balance toward the predominate TH2, which is associated with less allergy. Because the most common asthma trigger is allergy, Vitamin D's role is key in downregulating a patient's allergic sensitivities.

Studies demonstrate that Vitamin D modifies airway hyperresponsiveness by minimizing airway inflammation. Searing and Leung (2010) found that Vitamin D works to block inflammation in the airways by increasing

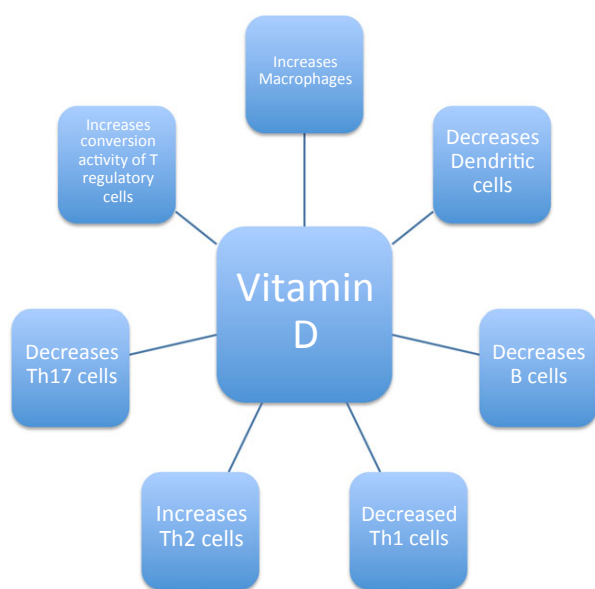


Figure 1 The immunomodulator role of Vitamin D.

interleukin-10 (a factor that reduces inflammation). Zosky et al. (2011) conducted a cross-sectional study in humans and found that low Vitamin D is associated with lower levels of lung function and reduced response to glucocorticosteroids. It is proposed that a possible mechanism of Vitamin D's benefit for asthma patients is an enhanced steroid responsiveness (Paul et al., 2012).

Vitamin D and childhood asthma

Vitamin D deficiency in children is an epidemic in the United States (Ali et al., 2009). It is theorized that the sustained burden of pediatric asthma in the United States may be a consequence of a Vitamin D deficiency (Litonjua, 2012). Vitamin D levels in children as young as the age of 6 are predictive of subsequent allergy/asthma-associated phenotypes at age 14 (Hollams, 2011).

Research links low Vitamin D with a 150% increased risk of asthma in U.S. children (Brehm et al., 2010). In this study, Vitamin D levels were measured in 1024 children with mild-to-moderate persistent asthma and 35% were found to have low Vitamin D levels. The researchers also found that low Vitamin D levels were associated with increased risk of asthma-related hospitalizations or emergency department visit (Brehm et al., 2010). Among those children in the study, African American children had the lowest Vitamin D levels, while Caucasian children had the highest. These results correlate with the prevalence of pediatric asthma in that African American children have a higher prevalence of asthma than

Table 1 Food sources of Vitamin D

FOOD	IU per serving
Salmon, cooked, 3 oz	1360
Mackerel, cooked, 3 oz	447
Tuna, canned in water, 3 oz	388
Orange juice, fortified, 1 c	137
Milk, fortified, 1 c	115–124
Yogurt, fortified, 6 oz	88
Egg, 1 (Vitamin D in yolk)	41

Caucasian children. This study lends credibility to the theory that low Vitamin D may be a key contributor to the sustained asthma burden in the United States.

Camargo et al. (2007) demonstrated that if a pregnant woman had Vitamin D deficiency, there was an increased risk for their child to develop asthma in the first years of life. This study suggests that maternal intake of individual nutrients may be a more important determinant of wheeze-associated illness developing in children than the mother's general dietary pattern. In similar research, Keet et al. (2011) demonstrated that low Vitamin D levels during pregnancy were inversely associated with wheezing and asthma after birth.

What is Vitamin D?

To the surprise of many, Vitamin D is not actually a vitamin but one of the oldest prohormones known to exist. As a prohormone (sometimes referred to as the pre-Vitamin D), a multistep conformational shift occurs to form Vitamin D, after which it is transported to the liver.

Vitamin D is a fat-soluble vitamin that occurs naturally in only a select few foods; for example, oily fish, fish liver oil, and egg yolk. Fortified foods provide most of the Vitamin D in the American diet. The United States mandates the fortification of infant formula with Vitamin D: 40–100 IU (international units)/100 kcal (kilocalorie). Table 1 contains a list of selected food sources of Vitamin D. Because foods contain low levels of Vitamin D, they have not been known to cause or contribute to Vitamin D toxicity (Hathcock, Shae, Vieth, & Heaney, 2007).

Forms of Vitamin D

While there are several forms of Vitamin D (D1, D2, D3, D4, and D5), the two major forms are D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D is measured in IU, where 1 IU is equal to only 0.000025 mg.

Supplemental Vitamin D is available as Vitamin D2 and Vitamin D3. Supplemental Vitamin D can be purchased in combination with other vitamins/minerals or by itself. Vitamin D3, as purchased over-the-counter, is the same

Table 2 Recommended daily allowance of Vitamin D

Age	Male	Female	Pregnancy	Lactation
0–12 months	400 IU (10 mcg)	400 IU (10 mcg)		
1–13 years	600 IU (15 mcg)	600 IU (15 mcg)		
14–18 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
19–50 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
51–70 years	600 IU (15 mcg)	600 IU (15 mcg)		
>70 years	800 IU (20 mcg)	800 IU (20 mcg)		

substance that is produced in human skin after sun exposure and is recognized as the “most natural” form of Vitamin D available.

There is a distinct difference between Vitamin D2 and D3 in that Vitamin D2 is not naturally present in the body and therefore has less binding capacity to Vitamin D receptors. Vitamin D3 is preferred over Vitamin D2 because it is less toxic to the body, more potent, and has a longer shelf. Vitamin D3 has been the most utilized form of Vitamin D used in research trials.

Measuring Vitamin D levels

Vitamin D3 serum level (calcidiol) is used to monitor a patient's Vitamin D level and establish diagnosis. The test is widely available, inexpensive, and does not require the patient fast prior to testing. Most experts agree that Vitamin D levels of at least 30 ng/mL, and upwards of 50 ng/mL, are optimal for preventive health. There are no current guidelines as to how often a patient's Vitamin D3 level should be checked. However, it is generally agreed that an annual to biannual check (depending on the patient's needs) is reasonable.

Vitamin D recommendations

There is no current consensus on a patient's optimal serum level or how to dose Vitamin D, as the science is continuing to emerge and evolve. However, there are several governing and medical specialty bodies that have published dietary intake recommendations. All are in agreement that Vitamin D dietary intake recommendations are based on age and modified by need. The National Food and Nutrition Board (FNB) has established the recommended dietary allowance for Vitamin D (see Table 2) (Ross, Taylor, Yaktine, & Del Valle., 2011). It is implied within these recommendations that no Vitamin

D synthesis is occurring from natural sunlight and that all of the patient's Vitamin D intake is from their diet.

The FNB recommends that a vitamin D deficient child (age 18 years and younger) be started on 1000 IU Vitamin D daily to raise their level to a minimum of 30 ng/mL. Similarly, those age 19 years and older should be supplemented with 1500–2000 IU Vitamin D daily with the same minimum goal of 30 ng/mL. The U.S. Endocrine Society recommends a 2–3 times higher dose of Vitamin D for obese patients because Vitamin D can be locked up in fat stores and the patients are at higher risk for deficiency. Interestingly, obesity is a risk factor for asthma, further supporting Vitamin D's role in increased asthma morbidity (National Heart, Lung, and Blood Institute [NHLBI], 2007).

There are various dosing methodologies being used by allergy and asthma experts in the United States, many of which have originated out of clinical experience and improved patient outcomes. Dr. Pinkus Goldberg, MD, FAAAAI, FAAAAI at Allergy Partners of Central Indiana in Indianapolis, Indiana (personal interview, April 10, 2012) reports clinical success in using a formula of dosing 100 IU of Vitamin D3 to raise the Vitamin D level in the patient 1 ng/mL. Dr. Goldberg, who has been in clinical practice for 30 years, states that he began using this formula after discussion with colleagues treating similar patients. Using this clinically based formula, a patient with a Vitamin D level of 10 would be started on Vitamin D3 2000 IU/day with the goal of raising the Vitamin D level to 30 ng/mL. If that same patient's Vitamin D goal was 40 ng/mL, an initial Vitamin D dose of 3000 IU/day would be given. Dr. Goldberg attributes the improved patient outcomes seen with using this Vitamin D formula to its reproducibility.

Signs of Vitamin D toxicity

Vitamin D toxicity is very rare. The initial and most notable symptoms of excess Vitamin D are hypercalciuria (excess calcium in the urine) and hypercalcemia (high blood calcium). Other symptoms that mark Vitamin D toxicity are nausea, vomiting, poor appetite, constipation, weakness, weight loss, tingling sensations in the mouth, confusion, and heart rhythm abnormalities. As mentioned, there is no risk of Vitamin D toxicity associated with sun exposure because of the body's negative feedback loop. The very rare instances of Vitamin D toxicity occur as supplemental Vitamin D bypasses the body's natural built-in protection system and excessive amounts are consumed over a period of time.

There is no consensus defining what is a toxic dose of Vitamin D. At present, most experts define a toxic level as that which causes symptoms of toxicity.

Hathcock et al. (2007) demonstrated that Vitamin D toxicity at a daily dose of 77,000 IU and acute overdose between 600,000 and 1,680,000 IU/day over a period of several days to months. A review of the literature reveals a specific case of Vitamin D toxicity that involved intake of over 2,000,000 IU per day (Koutkia, Chen, & Holick, 2001). Current research makes the case that it takes an extraordinary amount of Vitamin D to cause toxicity and/or overdose.

How is Vitamin D made?

When humans are exposed to natural sunlight, Vitamin D is manufactured. Accordingly, Vitamin D is nicknamed “the sunshine vitamin.” The body produces 10,000 IUs of Vitamin D₃ within minutes of full-body exposure to the sun (Holick, Chen, Lu, & Sauter, 2007). Patients are often curious to know if they spend copious amounts of time in direct sunlight, can they reverse a Vitamin D deficiency? The answer is “no.” The human cycle of Vitamin D synthesis operates as a negative feedback loop that provides a built-in safety mechanism to prevent toxic levels of Vitamin D being created when exposed to natural sunlight.

Patients should know that overexposing themselves to the sun is ill advised because of the documented risk of skin cancer. Because of the potential for mixed messages, a Vitamin D deficient patient should be advised to start supplementation as opposed to spending more time in the sun. Patients may be surprised to learn that it takes far less time in the sun for the body to make a day's supply Vitamin D than they would think. Patients may ask about the use of tanning beds as a source of Vitamin D. Studies demonstrate that the use of tanning beds increase Vitamin D levels (Tangpricha et al., 2004).

Vitamin D synthesis and skin type

A patient's skin type will determine the rate at which Vitamin D is synthesized in their body. Darker pigmented skin is less efficient in converting sunlight to Vitamin D because of the increased level of melanin—the skin's natural protection mechanism against excessive sunlight exposure. Skin types are categorized by numeric value scale: I (the lightest pigment) to VI (the darkest pigment).

Vitamin D synthesis occurs faster in individuals with lighter skin pigment than in those with darker pigmentation. Patients with type I skin only need about 15 min of sunlight to produce one daily requirement of Vitamin D. Patients with type V or VI skin need up to six times longer to produce the same daily requirement of Vitamin D. As patients age, their bodies are less efficient in making Vitamin D. In patients 60 years and older, it

can take up to four times longer to manufacture Vitamin D as for those under the age of 20 years. Skin loses 7-dehydrocholesterol, a necessary enzyme in the conversion process, with aging.

Who should be screened?

Vitamin D screening is recommended by the FNB for those who are *at risk* for deficiency: African American and Hispanic children and adults, pregnant and lactating women, those with limited sunlight exposure, those with malabsorption syndromes or osteoporosis, elderly patients, and those taking glucocorticosteroid medications for asthma and other diseases. Screening is also recommended for obese children and adults (BMI > 30). There is no evidence that shows a benefit for screening Vitamin D₃ levels in the asymptomatic population (Thatcher & Clarke, 2011).

Clinical application for NPs

NPs have long been focused on helping their asthma patients control their symptoms on the least amount of medication possible. Along with patient education, Vitamin D supplementation aids in achieving that goal. While there is no consensus on the use of Vitamin D as a mainstay in asthma treatment, research supports its consideration for use in asthma patients with low Vitamin D levels. Current evidence reinforces the need to measure Vitamin D levels for all asthma patients.

Summary

Vitamin D deficiency is an increasing health problem and has been linked to increased asthma symptoms and worsening asthma control. With an ever-increasing westernized population, more time is spent indoors and individuals have less exposure to sunlight. When individuals are outdoors, they are advised to cover their skin as best possible to minimize the risk for skin cancer. As a modern-day culture in the United States, more time is spent in front of computers and TVs than in generations past. Such changes put entire generations at risk for Vitamin D deficiency.

Vitamin D has a broad health benefit, including that for asthma. Studies show that in patients with severe, therapy-resistant asthma, lower serum Vitamin D levels are associated with lower lung function and asthma exacerbations, compared to control and patients with moderate asthma (Gupta et al., 2011). Although not currently included in the National Heart Lung and Blood Institute's National Asthma Education Prevention Plan asthma guidelines (NHLBI, 2007), Vitamin D has

been proposed to be a part of asthma treatment and management recommendations in future guideline revisions. More research is needed to clarify how low levels of Vitamin D affects asthma patients of all severity levels and to establish consensus on optimal dosing recommendations.

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