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Vitamin D in Atopic Dermatitis, Asthma and Allergic Diseases

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Synopsis

This review examines the scientific evidence behind the hypothesis that vitamin D plays a role in the pathogenesis of allergic diseases, with a particular focus on emerging data regarding vitamin D and atopic dermatitis. Both elucidated molecular interactions of vitamin D with components of the immune system, as well as clinical data regarding vitamin D deficiency and atopic diseases are discussed. The rationale behind the "sunshine hypothesis," laboratory evidence supporting links between vitamin D deficiency and allergic diseases, the clinical evidence for/and against vitamin D playing a role in allergic diseases, and the emerging evidence regarding the potential use of vitamin D in augmentation of the innate immune response in atopic dermatitis are reviewed.

Keywords

Vitamin D; atopic dermatitis; asthma; allergy

Introduction

Observations by Palm in 1890 and Sniadecki in 1922 of the lower prevalence of rickets in equatorial and rural populations respectively prompted both investigators to hypothesize that sun exposure was the reason for such a difference [1-3]. Subsequent work by Mellanby established cod liver oil as a cure for dogs with rickets [4] and experiments by McCollum demonstrated the existence of a vitamin within cod liver oil [5]. Both cod liver oil and sunlight exposure became known as treatment modalities for rickets. Foods containing cholesterol that were irradiated with light were also shown to cure rickets. Windhaus and colleagues subsequently discovered a cholesterol precursor, 7-dehydrocholesterol (7-DHC). Their Nobel Prize winning work showed that irradiation of 7-DHC with UV light induced formation of vitamin D_3 [1,6].

Humans receive at least 80% of their vitamin D through UV induced skin production [7,8]. According to the Environmental Protection Agency's National Human Activity Pattern

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Survey (NHAPS), 95% of Americans work indoors [9]. In addition, Americans spend only 10% of available daylight hours outside. One recent study found that during their time outdoors, Americans are exposed to 30% of the available ambient UV light secondary to conditions such as shade [9]. A similar study again using NHAPS data found that children and adolescents spend the same amount of time outside as adults (10% of the day). However, adolescents receive the lowest UV dose of any group [10]. Furthermore, the use of sunscreen with a sun protection factor of eight decreases cutaneous vitamin D production by 97.5% [7].

Data from the National Health and Nutrition Examination Survey (NHANES) from 2001-2004 has shown that, overall, sufficient levels of vitamin D were present in less than a quarter of the adolescent and adult U.S. population studied [11]. More recently, NHANES data looking at children found that 61% of subjects aged 1-21 years were vitamin D insufficient [12]. However, there are potential issues with the validity of the assay utilized for vitamin D data from NHANES. According to the Center for Disease Control and Prevention website, 25-hydroxyvitamin D (the main indicator of the body's vitamin D status as discussed below) data from the 2000-06 NHANES was likely affected by drifts in the assay performance over time [13]. In a group of patients ages 0-18 years with asthma, atopic dermatitis, and/or food allergy, our group has noted 48% of patients with insufficient (<30 ng/mL) levels of serum 25-hydroxyvitamin D (also referred to as 25(OH)D in the literature and referred to as just vitamin D hereafter unless being discussed in the context of metabolism) [14].

Data in adults suggests vitamin D levels less than approximately 30 ng/mL are associated with changes in parathyroid hormone levels, as well as intestinal calcium transport [8]. This has led some to argue that vitamin D levels between 20-30 ng/mL be considered vitamin D insufficient, although no consensus on optimal vitamin D levels exists [8]. A recent clinical report from the American Academy of Pediatrics changed the recommended dosage of vitamin D from 200 to 400 IU per day for all children (infants through adolescents) [15]. Typically, infant and child multivitamin and vitamin D preparations contain 400 IU per dose of vitamin D in either D_2 or D_3 form (see below). The report cites information from adult studies that have helped create the concept of serum vitamin D insufficiency. The Food and Nutrition Board has convened an expert committee to revisit the dietary reference intake for vitamin D and its report is expected to be released in May of 2010 [16]. Despite these new recommendations, there is concern that intake of 400 IU per day of vitamin D remains inadequate to promote sufficient levels of vitamin D and that the tolerable upper intake level of vitamin D can safely be increased [17]. Graded oral dosing of adults demonstrated that an eight-week course of 400 IU per day of vitamin D_3 raises the serum vitamin D concentration by only 4.4 ng/mL [18].

While the relationship of vitamin D deficiency and rickets is well established, only more recently has the role of vitamin D deficiency and insufficiency in allergic disease been debated. Prior to allergic disease entering the debate, epidemiologic research has described links between vitamin D and cancer, type I diabetes, and multiple sclerosis [8,19]. The International Study of Asthma and Allergies in Childhood (ISAAC) demonstrated the highest prevalence of asthma symptoms in countries such as the United Kingdom, Australia, New Zealand, and the Republic of Ireland [20]. This data helped form the foundation for the description that people living in more westernized, developed nations have higher reported rates of asthma, atopic dermatitis, and hay fever [21]. Studies in various Chinese cities with different socioeconomic profiles demonstrated the greatest amount of asthma and allergic symptoms in Hong Kong, the most westernized city studied [22]. Different authors have hypothesized that westernization, a lifestyle likely to be associated with greater time spent indoors, has fostered a propensity for vitamin D deficiency, which in turn has resulted in

more asthma and allergy [19,23]. The scientific evidence for this hypothesis will be reviewed.

Vitamin D Metabolism

Vitamin D enters the body through either the skin via cutaneous conversion of 7-DHC into pre-vitamin D_3 or the gut via food and/or supplement ingestion (see Figure 1) [8]. 7-DHC is converted into pre-vitamin D_3 by solar ultraviolet B radiation [8]. Sunlight also converts pre-vitamin D_3 and/or vitamin D_3 into inert products to prevent vitamin D intoxication [8]. Pre-vitamin D_3 isomerizes to vitamin D_3, is transferred to the dermal capillaries, and binds with vitamin D–binding protein (DBP) [24]. Ingested vitamin D utilizes chylomicrons and the lymphatic system for transportation to the circulation (Figure 1). Vitamin D from supplements can be ingested as either vitamin D_2 (ergocalciferol) from plant derived sources or vitamin D_3 (cholecalciferol) from animal derived sources. Vitamin D_3 is used to fortify several foods (see Table 1) in the United States, although few foods are fortified with vitamin D in Europe [8]. Vitamin D is also contained naturally in several species of fish and cod liver oil [24] (Table 1).

Vitamin D_3 (subsequently referred to as “D”) complexed with DBP is transported to the liver and is converted to 25-hydroxyvitamin D or 25(OH)D. 25-hydroxyvitamin D is released into the circulation, binds again to DBP, and is transported to the kidney where it undergoes further hydroxylation by the enzyme 25-hydroxyvitamin D-1 α-hydroxylase (CYP27B1) to 1,25-dihydroxyvitamin D or $1,25(OH)_2D$ (Figure 1). 25-hydroxyvitamin D levels are used to determine the body’s vitamin D status as this form has a longer half-life (2-3 weeks) than 1,25-dihydroxyvitamin D (4 hours) [24]. 1,25-dihydroxyvitamin D is the active form of vitamin D. Parathyroid hormone, calcium, phosphorus, fibroblast growth factor 23, and 1,25-dihydroxyvitamin D itself all influence the levels of 1,25-dihydroxyvitamin D through a variety of mechanisms (Figure 1). Finally, the enzyme 25-hydroxyvitamin D-24-hydroxylase (CYP24) catabolizes both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D into biologically inactive, water-soluble calcitroic acid [8].

The Effects of Vitamin D on the Immune System

The scope of vitamin D’s biological actions go beyond just calcium homeostasis and bone metabolism. The vitamin D receptor (VDR) was cloned in 1988 and shown to be a member of the nuclear receptor family [25]. VDR has been located in multiple tissues and cells in the human body, including peripheral blood mononuclear cells (PBMCs) and activated T lymphocytes [26]. VDRs are also located on dendritic cells (DCs), important antigen presenting cells [27,28]. The enzyme responsible for the synthesis of 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D-1-α-hydroxylase, is located on macrophages and DCs [29]. 25-hydroxyvitamin D-24-hydroxylase, which degrades 1,25-dihydroxyvitamin D, is also found in monocytes and macrophages [30]. Normal T and B-lymphocytes have been shown to express the vitamin D receptor after activation with phytohemagglutinin and Ebstein-Barr virus [31].

Further research has demonstrated that Vitamin D has multiple cytokine modulating effects through several different cells of the immune system. Tsoukas and colleagues in showed that picomolar concentrations of 1,25-dihydroxyvitamin D decreased IL-2 activity and inhibited the proliferation of mitogen-activated lymphocytes [32]. Mahon and colleagues showed that quiescent $CD4^+$ T cells, in addition to activated T cells, expressed VDRs [33]. Furthermore, 1,25-dihydroxyvitamin D decreased proliferation of both Th1 and Th2 cells, as well as lowered the production of IFN-γ, IL-2, and IL-5. In contrast, IL-4 production by Th2 cells was increased by 1,25-dihydroxyvitamin D [33]. Froicu and colleagues performed experiments with VDR knockout (KO) mice. In comparison to wild type (WT) mice, VDR

KO mice produced more IFN-γ. However, VDR KO mice also produced less IL-2, IL-4, IL-5 than WT mice [34]. Boonstra et al demonstrated that vitamin D inhibits IFN-γ production and promotes IL-4, IL-5, and IL-10 production in a mouse model [35]. These studies suggest that deficiencies in vitamin D levels and/or signaling would favor a predominant Th1 response and that the presence of vitamin D, while suppressing Th1 effects, also promotes Th2 respones.

Evidence also exists that vitamin D plays an inhibitory role in Th2 responses. In a murine model of pulmonary eosinophilic inflammation, early treatment with vitamin D supported allergen-induced T-cell proliferation along with IL-4, IL-13, and IgE production. However, the bronchoalveolar lavage fluid and lung tissue had impaired recruitment of eosinophils and low levels of IL-5 [36]. A study by Pichler and colleagues looked at the effects of 1,25-dihydroxyvitamin D on naïve $CD4^+$ T helper and $CD8^+$ cytotoxic T cells from human cord cell cultures. They found that 1,25-dihydroxyvitamin D had inhibitory effects in the naïve cells on IFN-γ production induced by IL-12, as well as IL-4 and IL-13 production induced by IL-4 [37]. This would suggest that vitamin D also helps blunt the Th2 response. Whether or not vitamin D favors a shift in the helper T cell balance toward Th1 versus Th2 dominance remains unclear. These variable results may be secondary to differences in the absolute amount of vitamin D exposure, the baseline vitamin D status (deficiency vs insufficiency vs sufficiency), and the timing of exposure (naïve versus mature cell lines). More likely, at pharmacologic levels, vitamin D may inhibit both Th1 and Th2 cell activation. Whether these known immune effects have translated into significant relationships between vitamin D levels and allergies, asthma, and atopic dermatitis is discussed below.

Vitamin D and Allergy

Several large birth cohort studies have examined the relationship between infant vitamin D supplementation and subsequent development of allergy and asthma. One study looked at a segment of the Northern Finland Birth Cohort from 1966 in which infants were supplemented with vitamin D in the first year of life. Mothers reported the frequency and dose of vitamin D supplementation and the daily dose of vitamin D was calculated based on this information. 83% of the subjects received 50 μg/day (2,000 IU/day) of vitamin D [38]. Subjects received several follow-ups, including at 31 years of age where the presence of asthma and atopy was assessed. After adjustment for social factors, the prevalence of atopy and allergic rhinitis at age 31 was higher in subjects who received vitamin D supplementation as infants [38]. Another prospective birth cohort of over 4,000 infants in whom 98% were supplemented with vitamin A and D (400 IU/day of vitamin D) in either a water-soluble or peanut oil form showed that infants who received water-soluble supplements had a greater risk of asthma, food hypersensitivity, and aeroallergen sensitization at age 4 than infants given peanut oil based supplements [39]. No significant associations were seen for eczema or allergic rhinitis [39]. However, additional prospective work looking at maternal vitamin D dietary intake during pregnancy by Camargo and colleagues demonstrated that women in the highest quartile of vitamin D intake had a lower risk of having a child with recurrent wheeze at 3 years of age [23]. These results may indicate that the timing of intervention in vitamin D levels may factor in subsequent allergic disease. An alternative explanation is that different absolute amounts of vitamin D have alternate physiologic effects on allergic pathogenesis. Furthermore, although beyond the scope of this review, vitamin D may also affect the body's susceptibility and response to infectious organisms, a major trigger of wheezing at a young age. The topic of vitamin D and infection in the setting of asthma has been reviewed elsewhere [40].

Several surrogate markers of vitamin D deficiency have been evaluated in the context of allergy and asthma prevalence. People living at higher latitudes are known to be at greater risk for vitamin D deficiency [24]. A review of 166 pediatric cases of clinical rickets from 1986 to 2003 commented that in the 5 studies involving rickets in white children, all involved subjects were from northern states [41]. People who live at northern latitudes above 35° are unable to synthesize vitamin D from November through February [8]. Given the variations in latitude in the United States that may contribute to differences in sun exposure, the potential exists to compare populations in various geographic environments with respect to allergic disease. An exploratory study on surrogate markers for vitamin D and EpiPen/EpiPen Jr (Dey, Napa, Calif) prescriptions revealed that states in the New England region had a higher prescription rate than southern states after controlling for socioeconmic factors [42]. A surrogate marker of sunshine exposure, melanoma incidence, was inversely correlated with EpiPen prescription rate, although average temperature and average precipitation were not [42]. An inverse relationship exists between body mass index and vitamin D status secondary to decreased bioavailability [8]. Prevalence of allergic disease in patients who underwent routine vitamin D screening as part of their care at an obesity clinic showed no association between vitamin D status and the prevalence of asthma or allergic rhinitis [43]. However, patients with vitamin D deficiency were more likely to report atopic dermatitis [43].

Vitamin D and Asthma

Of the different disorders associated with allergic inflammation, perhaps asthma has been the most closely examined in the context of vitamin D. Consistent with prior sections, evidence exists both in support and against vitamin D deficiency contributing to the asthma epidemic. Extensive reviews of both sides of the argument have been published previously [19,44].

Experimental models of asthma have been utilized to help test the vitamin D hypothesis. As mentioned previously, vitamin D has been shown in a murine model of eosinophilic inflammation to induce impaired recruitment of eosinophils and reduce levels of IL-5 [36]. Data is also emerging that vitamin D effects glucocorticoid signaling pathyways. Xystrakis and colleagues reported that the addition of vitamin D and dexamethasone to cultures of $CD4^+$ T regulatory cells from steroid resistant asthmatics enhanced IL-10 secretion from these cells to levels comparable from cells of steroid sensitive patients treated with dexamethasone alone [45]. Zhang and colleagues have also demonstrated that vitamin D enhances dexamethasone-induced MAP kinase phosphatase-1 (MKP-1) expression in peripheral blood mononuclear cells [46], a pathway by which glucocorticoids exert their anti-inflammatory effects. In patients referred to our institution with asthma, we have noted that serum vitamin D levels are inversely correlated with corticosteroid usage [14]. These laboratory and clinical observations raise the question of vitamin D supplementation potentially having a steroid sparing effect in asthma.

While the studies mentioned in the prior paragraph suggest a supportive role for vitamin D in asthma control, some experiments in KO mice do not support this association. Experimental allergic asthma induction was performed by Wittke and colleagues in VDR KO and WT mice. The WT mice developed asthma, as expected. However, VDR KO mice failed to develop asthma after allergen induction. The administration of 1,25-dihydroxyvitamin D to WT mice had no effect on asthma severity, but did increase expression of two Th2-related genes [47]. Some studies have described an association between VDR genetic polymorphisms and asthma, but this has not been replicated in subsequent experiments [19].

Several clinical studies exist supporting a positive relationship between vitamin D status and asthma (see Table 2). An analysis of over 14,000 patients age 20 and above using the NHANES database between 1988-1994 showed that subjects whose vitamin D level was in the highest quintile had significantly higher FEV_1 and FVC [48]. A recent paper on children with asthma from Costa Rica showed a significant association between rising vitamin D levels and reduced use of antiinflammatory medication in the previous year [49].

Conflicting data exists on the influence of maternal vitamin D status and subsequent development of asthma. As mentioned previously, maternal intake of vitamin D has been associated with lower prevalence of wheezing at 3 years of age [23]. Another birth cohort from Scotland with information on maternal vitamin D intake had outcome measures analyzed at 5 years of age. The highest quintiles of maternal vitamin D intake were associated with reduced risk for ever wheezing, wheezing in the previous year, and persistent wheezing at ages 2 and 5 [50]. Associations were independent of the children's vitamin D intake. Interestingly, despite the wheezing associations, maternal vitamin D intake was not associated with asthma at age 5. In addition, maternal vitamin D intake was not associated with lower spirometry values or atopic sensitization [50]. A group of children from the United Kingdom were followed prospectively after vitamin D levels from their mothers were collected during pregnancy. The investigators found an increased risk of eczema at 9 months and asthma at 9 years in children whose mother's had a vitamin D level >75 nmol/L (>30 ng/mL), although only 30% of patients were available for follow up at 9 years [51].

Vitamin D and Atopic Dermatitis

A large amount of data has emerged regarding the molecular effects of vitamin D in the skin. VDR expression in the skin was first confirmed after rats injected with radio-labeled 1,25-dihydroxyvitamin D demonstrated radioactivity concentrated in the nuclei of the epidermis along with a variety of other tissues [52]. 1,25-dihydroxyvitamin D has been shown to enhance keratinocyte differentiation, as well as have either stimulatory or suppressive effects on keratinocyte growth that is concentration dependent [53]. VDR expression on keratinocytes appears to be present only in proliferating cells and consequently, the basal keratinocyte is the main VDR containing cell in the epidermis. Variable VDR expression based on the proliferating and differentiating state of the keratinocyte, as well as local cytokine-mediated interactions may provide an explanation for vitamin D's observed inhibitory effects in psoriatic skin and proliferative effects in normal skin [53]. Vitamin D has been shown to increase synthesis of PDGF promoting wound healing, and TNFα promoting keratinocyte differentiation [54,55]. Decreased synthesis of IL-1α, IL-6, and RANTES secondary to vitamin D has resulted in decreased inflammation in epidermal keratinocytes [56-58]. Both the enzyme responsible for the intial hydroxylation of vitamin D to 25-hydroxyvitamin D, as well as the enzyme responsible for the conversion of 25-hydroxyvitamin D into active CYP27B1 are found in keratinocytes [59]. Vitamin D has also been demonstrated to have a beneficial effect on the permeability barrier in the epidermis. Bikle and colleagues studied mice null for the expression of 25-hydroxyvitamin D-1α-hydroxylase (1OHase). Lower levels of multiple proteins necessary for formation of the stratum corneum, including filaggrin, were lower in the null mice compared to the wild-type controls [60]. Following tape disruption, null mice had a significantly delayed barrier recovery compared to wild type mice [60].

As mentioned previously, VDRs are located on macrophages and DCs, as is CYP27B1. 1,25-dihydroxyvitamin D has been shown to have inhibitory effects on the differentiation of DCs [28]. *In vitro* treatment of DCs with vitamin D leads to decreased IL-12 and enhanced IL-10. These cytokine effects, along with inhibitory effects on DC maturation, promote

tolerogenic properties and suppressor T cell induction [28]. A short treatment course of 1,25-dihydroxyvitamin D in mice induced tolerogenic DCs and increased T regulatory cells [61].

The pathogenesis of atopic dermatitis involves both epidermal barrier and immunologic dysfunction. Atopic dermatitis patients can have defects of both the permeability barrier and the antimicrobial barrier of the stratum corneum [62]. The permeability barrier consists of hydrophobic lipids that percolate the extracellular environment of the stratum cornuem and prevent water loss into the outside environment [62]. Overactivity of serine proteases secondary to genetic defects, such as filaggrin and environmental stimuli, such as alkaline soaps, promotes reduction of hydration and extracellular lipids in the stratum corneum, introduction of antigens, and promotion of inflammation [62]. Loss of function mutations in the gene encoding filaggrin (FLG, located on chromosome 1q21 in a locus termed the epidermal differentiation complex) are associated with atopic dermatitis [63] (see also article by Irvine and O'Carrol in this issue). Population based studies in European children show a 3-fold increased risk for atopic dermatitis in subjects with FLG variants and 18 to 48% of patients with atopic dermatitis carry a FLG null allele [64].

An important part of the antimicrobial barrier are antimicrobial peptides (AMPs). AMPs are secreted on the surface of the skin as a first-line defense against infection. The release of AMPs can be triggered by toll-like receptors (TLRs). AMPs are secreted by many different cells in the skin, including keratinocytes and mast cells. Aside from their antimicrobial properties, they are thought to play a role in immune system signaling [65]. Cathelicidin is one of the most well known AMPs. Cathelicidin deficiency in the skin is known to be associated with atopic dermatitis. Ong et al, demonstrated significantly decreased immunostaining for cathelicidins in acute and chronic atopic dermatitis lesions compared to psoriatic skin lesions [66]. This finding supports the differences in skin infections between patient with these two diseases. Amongst patients with atopic dermatitis, those with a history of herpes simplex virus (HSV) superinfection have significantly lower cathelicidin levels [67]. Antiviral assays have shown that cathelicidin has activity against HSV [67]. Skin from cathelicidin deficient mice has also been shown to have reduced ability to limit vaccinia virus proliferation [68]. A mulitcenter study to determine phenotypes associated with eczema herpeticum (ADEH) showed that ADEH patients were more likely to experience cutaneous skin infections and have more Th2 polarized disease [69].

Vitamin D has been shown to have a significant role in cathelicidin expression in the skin [65]. Wang and colleagues demonstrated that promoters of cathelicidin and beta2 defensin (another AMP) genes contain consensus vitamin D response elements and that 1,25-dihydroxyvitamin D promotes antimicrobial peptide gene expression [70]. Liu and colleagues reported that activation of toll-like receptors by *M. tuberculosis*–derived lipopeptide resulted in increased expression of both VDR, as well as CYP27B1 (the enzyme responsible for conversion of vitamin D into the active form) causing cathelicidin induction [71]. Therefore, it has been proposed that skin infection or injury leads to activation of CYP27B1 and upregulated VDR expression, which in turn leads to increased production of activated vitamin D and antimicrobial peptides [65,71].

Given the potential for vitamin D to suppress inflammatory responses, enhance antimicrobial peptide activity, and promote the integrity of the permeability barrier, supplementation provides a possible therapeutic intervention for a variety of skin disorders, including atopic dermatitis. In a sample of 14 patients with moderate to severe atopic dermatitis who received 4,000 IU/day of vitamin D_3 for 21 days, biopsied lesional skin showed a significant increase in cathelicidin expression [72]. A double-blind randomized controlled trial in children with winter-related atopic dermatitis (primarily mild) was

performed utilizing a regimen of 1,000 IU/day of vitamin D for one month during the winter. Five subjects received supplementation versus placebo in six subjects. Baseline changes in global assessments of skin showed that the vitamin D treatment group had a significant improvement in baseline score compared to placebo [73]. Future trials involving larger sample sizes and longer treatment periods will be necessary to more fully assess vitamin D as a therapeutic strategy in atopic dermatitis.

Summary

Vitamin D insufficiency data is expanding to include evidence on its role in asthma, allergic disorders, and atopic dermatitis. In addition to its well-documented relationship with rickets and bone metabolism, vitamin D is now recognized as an immunomodulator. However, conflicting data exists with respect to the role of vitamin D in the pathogenesis of allergic diseases. Future research on vitamin D supplementation will help determine if the sunshine vitamin can serve as an adjuvant treatment for asthma and atopic dermatitis.

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Abbreviations

1OHase	25-hydroxyvitamin D-1α-hydroxylase
25(OH)D	serum 25-hydroxyvitamin D
7-DHC	7-dehydrocholesterol
ADEH	eczema herpeticum
AMPs	antimicrobial peptides
CYP24	enzyme 25-hydroxyvitamin D-24-hydroxylase
CYP27B1	enzyme 25-hydroxyvitamin D-1α-hydroxylase
D	vitamin D_3
DBP	vitamin D–binding protein
DCs	dendritic cells
HSV	herpes simplex virus
ISAAC	International Study of Asthma and Allergies in Childhood
KO	knockout
MKP-1	MAP kinase phosphatase-1
NHAPS	EPA's National Human Activity Pattern Survey
PBMC	peripheral blood mononuclear cells
TLRs	toll-like receptors
VDR	vitamin D receptor
WT	wild type mice

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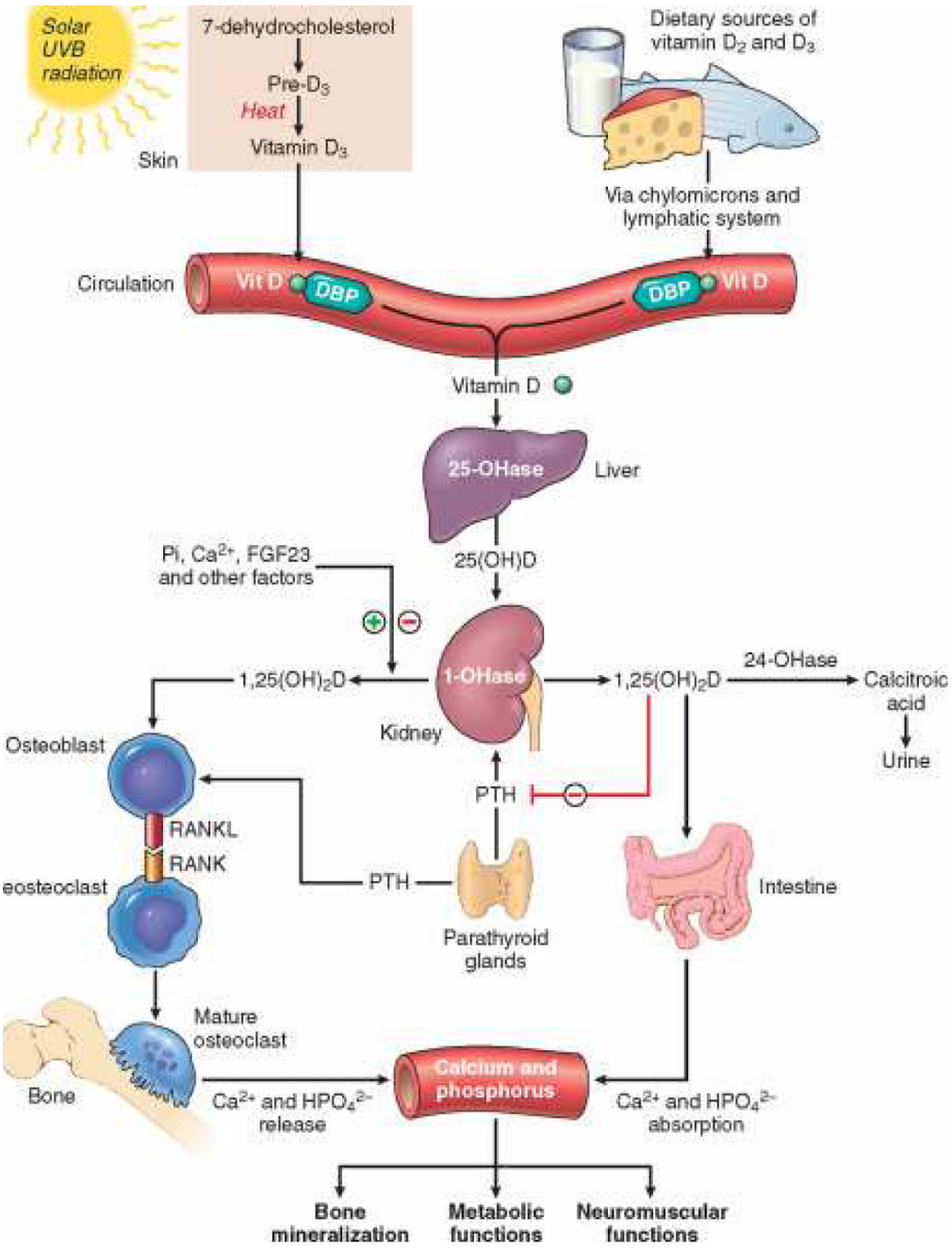

Figure 1. Vitamin D Metabolism

Vitamin D is produced from 7-dehydrocholesterol in the skin or is ingested in the diet. It is converted in the liver into 25(OH)D, and in kidney into $1,25(OH)_2D$ (1,25-dihydroxyvitamin D), the active form of the vitamin. $1,25(OH)_2D$ stimulates the expression of RANKL, an important regulator of osteoclast maturation and function, on osteoblasts, and enhances the intestinal absorption of calcium and phosphorus in the intestine. DBP, vitamin d-binding protein (α1-globulin).

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Table 1

Vitamin D Content of Foods

Food	Amount	Vitamin D Content (IU)
Cod Liver Oil, 1 tablespoon	1 tablespoon	1,360
Salmon, cooked, 3.5 ounces	3.5 ounces	360
Mackerel, cooked, 3.5 ounces	3.5 ounces	345
Sardines, canned in oil, drained	1.75 ounces	250
Tuna Fish, canned in oil	3 ounces	200
Milk, vitamin D-fortified	1 cup	98
Margarine, fortified	1 tablespoon	60
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D	0.75-1 cup	40
Egg, whole	one	20
Liver, beef	3.5 ounces	15
Cheese, Swiss	1 ounce	12

Adapted from http://dietary-supplements.info.nih.gov/factsheets/vitamind.asp#h3. Office of Dietary Supplements, National Institutes of Health. U.S. Department of Agriculture, Agricultural Research Service. USDA Nutrient Database for Standard Reference, Release 21, 2009, Table 3.

Table 2

Summary data on Vitamin D and Asthma and/or Recurrent Wheeze

Investigator	Population Studied	Results	Reference
Black et al.	>14,000 adults using the NHANES database	↑FEV_1 and ↑FVC in subjects whose vitamin D level was in the highest quintile	48
Brehm et al.	Asthmatic children from Costa Rica	Log_{10} ↑ in vitamin D level associated with ↓hospitalizations, ↓antiinflammatory medication, and ↓markers of allergy	49
Camargo et al.	Mother-child pre-birth cohort	Mothers in highest quartile of vitamin D intake had lower risk for child at age 3 with recurrent wheeze	23
Devereux et al.	Mother-child pre-birth cohort	Mothers in highest quintile of vitamin D intake had lower risk for child at age 5 to have ever wheezed, wheezing in the previous year, and persistent wheezing. No association of vitamin D levels with asthma, spirometry, or atopic sensitization.	50
Gale et al.	Mother-child pre-birth cohort	Maternal 25(OH)D concentrations above 30 ng/mL associated with an ↑risk of eczema at 9 months and ↑risk of asthma at 9 years	51