Vitamin D Status and Allergy Outcomes

Subjects: Allergy

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The very early onset of allergic diseases points to the specific vulnerability of the developing immune system to environmental changes and the development of primary intervention strategies is crucial to address this unparalleled burden. Vitamin D is known to have immunomodulatory functions. While allergic disease is multifactorial, associations with reduced sunlight exposure have led to the hypothesis that suboptimal vitamin D levels during critical early periods may be one possible explanation. Interventions to improve vitamin D status, especially in early life, may be the key to allergic disease prevention.

Keywords: vitamin D ; non-communicable disease ; allergic disease

1. Environmental Factors as Causes for the Global Rise of Vitamin D Deficiency and Sources of Vitamin D

Considering that up to 90 to 95% of vitamin D can be provided by cutaneous synthesis under the influence of UVB light [1], the major cause for the vitamin D deficiency pandemic is a lack of appreciation that UV light exposure is the major physiological source of vitamin D [2][3][4]. Increased time spent indoors due to the exponential rise of indoor employment and relaxation activities (particularly an increase in screen time) in modern times as well as sun protection behaviours [5][6][7] are lifestyle factors which have an influence on UV light exposure. In addition, lower UVR levels are found in high-latitude locations and winter season. Furthermore spending time outdoors exclusively in the morning or after 3 p.m. leads to reduced UV light expsosure [8].

Considering physiological factors, increased skin pigmentation [9][10], aging and obesity have an influence on vitamin D status [6]. Low dietary vitamin D intakes caused by changes in nutrition from more traditional vitamin D-containing food sources to modern commercial, highly processed fast food can contribute to vitamin D deficiency by destroying the naturally contained vitamin D.

Vitamin D occurs in two forms: vitamin D2 and vitamin D3. Vitamin D2 is obtained from the UV irradiation of the yeast sterol ergosterol and is found in sun-exposed and sun-dried mushrooms. Vitamin D3 is found in oil-rich fish such as herring, salmon and mackerel, tuna, cod liver oil and egg yolk [1]. People living in the far southern or northern latitudes may also obtain vitamin D from seal blubber, whales or polar bear liver [3]. In addition, foods enriched with fortified vitamin D [1] and nutritional supplements play a role in maintaining a sufficient vitamin D status.

2. Vitamin D Metabolism and Physiology

Vitamin D is a pre-hormone which historically plays a critical role in calcium and mineral homeostasis, bone modeling and remodeling. However, the role of vitamin D goes far beyond this, as different activities of vitamin D ensure proper functioning of vital human organs including the skin [11]. Apart from functioning *on* the skin, vitamin D is also predominantly derived *from* the skin via sun exposure, which makes vitamin D unique among hormones [1][12][13].

During sun exposure, 7-dehydrocholesterol in the skin absorbs UVB radiation and undergoes chemical rearrangements to form the thermodynamically stable vitamin D3 [8]. Vitamin D2 and D3 act as pro-hormones and, when activated, have the same biological activity. Following ingestion or transport from the skin to the circulation, these calciferols are bound to the vitamin D-binding protein (DBP) [14]. DBP transports the calciferols to the liver, where the first step of hydroxylation to 25-hydroxyvitamin D (25(OH)D) takes place [15].

While 25(OH)D is the predominant circulating metabolite, it is largely inert and displays minimal binding affinity to the vitamin D receptor (VDR) [15]. Hence, to gain biological activity in a second step, 25(OH)D must undergo further renal hydroxylation [15]. 1,25$(OH)_2$D (calcitriol) is the active metabolite of vitamin D which is bound to DBP while circulating in the blood and transported to the VDR. After transport to the VDR, 1,25$(OH)_2$D is released to dock on the VDR and induce

processes in the cell nucleus [1][16]. However, 1,25$(OH)_2$D is not used as a measure of vitamin D status [17] due to its short circulating half-life time (4 h), low serum concentrations and tight regulation [17]. Instead, 25(OH)D is used to evaluate vitamin D status as it has a long half-life time (2–3 weeks), provides stable serum concentrations and is present at concentrations approximately 1000-fold greater than 1,25$(OH)_2$D [17]. The international Endocrine Society's guidelines define vitamin D deficiency as 25(OH)D < 50 nmol/L (<20 ng/mL), and vitamin D insufficiency as <75 nmol/L (<30 ng/mL) [17].

More recent research revealed that calcitriol modulates activation, proliferation and differentiation of immune and inflammatory cells through the VDR expressed on these cells [18][19][20][21][22]. Apart from immune cells [22], the VDR is also present on cells of the skin [23] and cardiovascular system [24], and these functions may provide some explanation for the epidemiological associations between vitamin D status and NCDs including cardiometabolic conditions, malignancies and immune disorders [25].

3. Vitamin D Receptor and Vitamin D-Binding Protein Polymorphisms and Links to Allergic Diseases

The VDR is a member of the nuclear receptor family of transcription factors and is found on most cells of the human body including skin cells (basal layer of the epidermis, keratinocytes and hair follicles) [26] and immune cells, with effects on cell differentiation, proliferation and apoptosis [27]. It is therefore quite feasible that VDR polymorphisms on interaction with environmental factors could significantly influence immune regulation by altering cell proliferation and differentiation [28]. Genetic studies have provided early evidence of a potential role of the VDR in the genesis of allergic diseases. Looking at the link to asthma specifically, the association between a number of VDR restriction fragment length polymorphisms and the risk of asthma has been described [29]. However, other studies could not confirm the role of VDR polymorphisms on allergy outcome [30][31]. Tamasauskiene et al. conclude that the association of VDR gene polymorphisms and vitamin D with asthma, allergic rhinitis and atopy is variable [32]. The inconsistency between findings may be due to different study designs, but also likely reflects that allergic diseases are complex, involving multiple genetic and environmental factors [29][32].

There are numerous other genes involved in the vitamin D metabolism pathway that have been associated with the risk of allergic disease [33][34][35]. DBP polymorphisms and vitamin D deficiency may jointly or independently contribute to a variety of skeletal and non-skeletal adverse health outcomes including different NCDs such as osteoporosis, diabetes, thyroid autoimmunity, inflammatory bowel disease, chronic lung disease [36] and allergy development [37][38]. The exact role of DBP in the pathophysiology of all these inflammatory diseases is, however, not completely understood. Additionally, as in other genetic associations, the influence of DBP on allergic diseases is likely to be affected by gene–gene and gene–environment interactions.

4. Immunoregulatory Functions of Vitamin D and the Influence on Allergic Disease Development

A link between vitamin D and the immune system was first acknowledged approximately four decades ago with the expression of the VDR in both activated T and B cells [22]. Since then, the body of evidence suggesting that vitamin D, especially its active metabolite, plays a key role in modulating the physiological activity of the immune system has grown.

4.1. The Role of Vitamin D in the Th1/Th2 Dichotomy

Early experiments showed that the active metabolite 1,25$(OH_2)D_3$ inhibits interleukin (IL)-2 production and T-cell proliferation [22][39]. Th (T-helper) cells are a primary target for 1,25$(OH)_2$D, suppressing Th cell proliferation through decreased Th1 cytokine production of these cells [40][41][42].

In the first instance, actions such as this would not seem to be beneficial for the genesis of allergic diseases. However, it needs to be considered that the immunosuppression of Th1 is not associated with an increase in pro-inflammatory Th2 cytokine production [43][44]. Indeed, an Austrian study showed that in cluster of differentiation $(CD)4^+$ cord blood (CB) cells, 1,25$(OH)_2D_3$ suppressed Th2-driven IL-4 and IL-13 expression. Hence, 1,25$(OH)_2D_3$ induced a T-cell population without further predominance of Th2-related cytokines. It was concluded that predominantly naïve cells have a balanced effect on cytokine production, inhibiting both Th1 and Th2 cytokines [44].

4.2. Immunomodulatory Function of Vitamin D on T Regulatory Cells and Allergic Disease

Development

Another group of T cells known to be potentially induced by 1,25 $(OH)_2D_3$ are regulatory T cells (Treg) [45]. Allergic disease reflects a failure to develop immunotolerance and although a part of the Th family, Treg cells act to *suppress* immune responses by other T cells and are essential in controlling inflammation and promoting tolerance to allergens.

The majority of Treg arise in the thymus. These $CD4^+FOXP3^+$ natural regulatory T cells (nTreg) mediate tolerance to self-antigens [46]. A second population of $CD4^+FOXP3^+$ Treg develop in peripheral lymphoid tissues from naïve conventional $CD4^+FOXP3^+$ T cells after exposure to antigens in combination with Transforming Growth Factor (TGF)-beta [47]. These cells are called induced regulatory T cells (iTreg) and are predominantly found within environmental interfaces such as lung respiratory mucosa and the intestines during chronic inflammation activities against microbial agents or importantly environmental (e.g., food and airborne) allergens [48][49]. Both subsets, nTreg and iTreg, play a key role in maintaining peripheral tolerance [50].

Due to the strong associations between Treg and allergic diseases [51][52][53][54], identification of factors which may influence the number and function of Treg is crucial. Interestingly, vitamin D appears to influence Treg activity and differentiation [55], suggesting an influence on allergic disease and asthma outcome [55][56].

There is considerable evidence in animal studies that vitamin D3 stimulates dendritic cells (DCs), which in turn may induce IL-10-producing $CD4^+$ T cells and antigen-specific Treg [57]. High levels of $1,25(OH)_2D$ have been shown to induce the lineage-specific FOXP3 transcription factor, which is essential for the development and functioning of Treg [58][59] by enhancing the number and activity of circulating $CD4^+$ Treg and their anti-inflammatory functions [60][61][62]. A recent study by Gorman et al. found that topical application of vitamin D in mice suppressed skin swelling in response to mechanisms that may be dependent on mast cells and Treg [63].

4.3. Antigen-Presenting Cells and Dendritic Cells

Antigen-presenting cells (APCs) play a significant role in the Th1/Th2 paradigm of autoimmune and allergic disease [64] and allergic disease development [65][66]. As on many other cell types, the VDR is expressed on APCs. However, beyond this DC [67], monocytes and macrophages [68] can produce 25(OH)D3 with subsequent local effects.

Different DC subsets have been identified on sites which are frequently involved in allergic reactions such as the skin, and the respiratory and gastrointestinal tracts. For at least a decade, vitamin D3 has been suggested to program DCs for tolerance by reducing their capability to activate and generate T cells, while increasing their potential to upregulate Treg and altering receptor expression [69]. Treatment of DCs with 1,25(OH)D3 showed decreased production of pro-inflammatory cytokines (e.g., interferon (IFN)-α and IL-12) and increased production of the anti-inflammatory cytokine IL-10 [70].

In addition to being targets of vitamin D3, DCs can generate 1,25(OH)D3 locally to influence T-cell programming [69]. The primary function of DCs is to initiate and refine adaptive immune responses, highlighting them as a potential therapeutic tool in diseases with skewed T-cell responses, including allergic diseases. Hence, adequate 25(OH)D3 levels through preventing/correcting vitamin D deficiency may facilitate a tolerogenic, anti-inflammatory immune profile.

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