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Immunomodulatory Effect of Vitamin D in Children with Allergic Diseases

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Abstract

The discovery that many cells express vitamin D receptors and the recognition of widespread vitamin D insufficiency has stimulated interest in the potential role of vitamin D in nonskeleton conditions. There is an increasing evidence to support the role of vitamin D pathway in the regulation of the function of both innate and adoptive immune systems. Vitamin D regulates immune function by inhibiting the differentiation and maturation of human dendritic cells, enhancing interleukin (IL)-10 and tumor growth factor- β (TGF- β) secretion and inhibiting T-cell functions. Vitamin D has the ability to suppress inflammatory cytokines, such as tumor necrosis factor (TNF), interleukin-1 (IL-1), interferon gamma (IFN- γ), and interleukin-2 (IL-2), while it increases the generation of anti-inflammatory cytokines IL-4 and IL-10. In B cells, vitamin D3 has also been shown to suppress immunoglobulin E (IgE) antibody class switch partly through the inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B).

Keywords: allergic diseases, vitamin D, vitamin's D role, metabolism, implication on immune system

1. Introduction

Vitamin D deficiency has been proposed as a potential contributing factor in patients with allergic diseases. It has been shown that serum levels of vitamin D correlate with pulmonary function, asthma onset, and the development of allergic diseases. Based on clinical and observational

data, the plasma level of 25-hydroxyvitamin D may serve as a “marker” to detect or define a subclinical deficiency of vitamin D.

Its possible role in immunotherapy has also been studied. Natural activity of vitamin D seems to be highly attractive in the context of the mechanism and clinical effect of subcutaneous immunotherapy (SIT); however, its role in sublingual immunotherapy (SLIT) is still undefined. Vitamin D enhances interleukin (IL)-10 production by CD4⁺ T cells and enhances sublingual immunotherapy efficacy in a murine asthma model. Recently, Heine et al. showed that 25-hydroxyvitamin D₃ promotes the long-term effect of specific immunotherapy in a murine allergy model; their findings were paralleled by reduced Th2 cytokine expression in the lungs. They observed that vitamin D deficiency promotes the development of type I sensitization and correction of its serum concentrations enhances the benefit of specific immunotherapy.

2. Vitamin D metabolism

Vitamin D refers to a group of fat-soluble corticosteroids responsible for enhancing intestinal absorption of calcium, iron, magnesium, phosphate, and zinc. In humans, the most important compounds in this group are vitamin D₃ (also known as cholecalciferol) and vitamin D₂ (ergocalciferol).

There are two ways in which vitamin D₃ (cholecalciferol) is normally provided to human body:

1. It may be produced in the skin as a result of ultraviolet irradiation of 7-dehydrocholesterol (previtamin D), which is slowly isomerized to vitamin D₃ [1, 2].
2. It is also derived from the diet in fish (vitamin D₃) and in plants (mainly vitamin D₂); vitamin D₂ is derived from irradiation of ergosterol, which occurs to some degree in plankton or plants under natural conditions [1].

Both vitamin D₃ and vitamin D₂ are inactive in many biological systems and must undergo a series of metabolic transformations before exerting effects in target tissues [1–3].

The prohormone vitamin D₃ is produced in the skin through ultraviolet irradiation of 7-dehydrocholesterol, then to make it biologically active the prohormone vitamin D is transported in the blood by the vitamin D binding protein (DBP) to the liver, where it is metabolized to 25-hydroxyvitamin [4]. In the liver, vitamin D is hydroxylated at C-25 by cytochrome P 450 vitamin D 25-hydroxylases, resulting in the formation of 25-hydroxyvitamin D (25(OH)D₃). This is the major circulating metabolite of vitamin D in plasma, and its measurements are used to provide an index of vitamin D nutritional status [2, 3]. Based on the evidence in the clinical trials and meta-analyses, the workgroup concluded that a serum 25 hydroxyvitamin D concentration of 30 ng/mL (75 nmol/L) should be a minimum goal to achieve in adults and children [5–7]. The best outcomes were seen with 25(OH) levels from 36 to 40 ng/mL (90–100 nmol/L) [6–8].

However, 25(OH)D₃ itself is metabolically inactive and must be modified before function [3]. On the next metabolic step, 25(OH)D₃ is transported by DBP to the kidney, where in the proximal renal tube it is hydroxylated at the position C1 (position of carbon 1), resulting in the hormonally active form of vitamin D 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃), which is responsible for most of the biological actions of vitamin D [4]. As a result of 1 and 25 hydroxylation, the prohormone vitamin D is being structurally transformed into an active hormone.

The best known target organ effects of 1,25(OH)₂D₃ are on the intestine to stimulate absorption of calcium and phosphate, next on bone to cause release of calcium and phosphate. It has been proved that there exists a negative feedback mechanism with the hormonal systems (parathyroid hormone, prolactin, and growth hormone) and the effect of 1,25 (OH)₂D₃ [1, 2].

Beside 1,25(OH)₂D₃, the kidney can also produce 24,25 dihydroxyvitamin D₃ (24,25(OH)₂D₃), a relatively inactive metabolite comparing to 1,25 (OH)₂D₃. The metabolite 24,25 (OH)₂D₃ is produced by 24 hydroxyvitamin D₃ 24 hydroxylase from both substrates: 25(OH)D₃ and 1,25 (OH)₂D₃ [4, 9]. This enzyme 24(OH)D₃ 24 hydroxylase limits the amount of 1,25(OH)₂D₃ in target tissues by accelerating the catabolism of 1,25 (OH)₂D₃ and by decreasing the amount of 25(OH)D₃ available to 1 hydroxylation [4]. Summarizing the main role of 24(OH)lase is vitamin D inactivation.

3. The mechanism of action of vitamin D

The vitamin D functions through a single vitamin D receptor (VDR). It is classified as a steroid hormone, related to the retinoic acid receptors and as most of the receptors has a DNA-binding domain (called C-Domain), a ligand-binding domain (called E-domain), and finally activating domain (called F-domain) [1]. It has been proved that a single receptor mediates all of the functions of vitamin D. This receptor is a 427 amino acid peptide and acts through vitamin D-responsive elements (VDREs), which are placed on the start site of the target gene [1].

VDR was proved to be found in almost all tissues and cells. It has been established that the diverse biological actions of 1,25-dihydroxyvitamin D₃ are initiated through precise changes in gene expression, which are mediated by an intracellular VDR. Activation of the VDR through direct interaction with 1,25(OH)₂D₃ prompts the receptor's rapid binding to regulatory regions of target genes, where it acts to nucleate the formation of large protein complexes whose functional activities are essential for directed changes in transcription. When VDR interacts with the ligand, the repressor is no longer able to bind the receptor and the receptor changes conformation, forming heterodimer at the VDREs [1, 10]. At the same time, it binds several other proteins required in the transcription complex and acquires an activator [1, 10]. Once the complex is formed, DNA bends, biochemical processes take place, and transcription is either initiated or suppressed depending on the gene [1, 10, 11]. These responses are tissue-specific and range from highly complex actions essential for homeostatic control of mineral metabolism to focal actions that control the growth, differentiation, and functional activity of numerous cell types including those of the immune system, skin, the pancreas, and bone.

4. Physiological effects of vitamin D

Vitamin D is well known as a hormone involved in mineral metabolism and bone growth. Its main effect is to facilitate intestinal absorption of calcium; however, it also stimulates absorption of phosphate and magnesium ions. In cases when there is a lack of vitamin D, dietary calcium is not absorbed efficiently. Vitamin D stimulates the expression of a number of proteins involved in transporting calcium from the lumen of the intestine, across the epithelial cells and into blood. The best studied of these calcium transporters is calbindin, an intracellular protein that carries calcium across the intestinal epithelial cell [12].

Vitamin D-dependent calcium-binding proteins (calbindin-D) are the major proteins involved in intracellular calcium transport in the intestine and the kidneys. In mammals there are two classes of calbindin-D: the 9000-dalton calbindin (calbindin-D9k) and the 28,000-dalton calbindin (calbindin-D28k). First identified in the intestine, calbindin-D9k is also expressed in the kidneys, the placenta, the yolk sac, and the lungs. The expression of calbindin-D9k and calbindin-D28k in the intestine and kidneys has been shown to be regulated by $1,25\text{-(OH)}_2\text{D}_3$ in animal models as well as in cell and organ cultures [13].

In several studies it has been shown that the regulation of calbindin-D9k and calbindin-28k by $1,25\text{-(OH)}_2\text{D}_3$ involve both transcriptional and posttranscriptional mechanisms [12, 13]. It can also be found in other tissues (brain, placenta, and lungs); however, calbindin-D genes have not been shown to be regulated by $1,25\text{-(OH)}_2\text{D}_3$ [14], suggesting that the regulation of calbindin-D gene expression by $1,25\text{-(OH)}_2\text{D}_3$ involves tissue-specific factors.

There is evidence that calcium may also modulate the actions of $1,25\text{-(OH)}_2\text{D}_3$ on calbindin gene expression. *In vitro* experiments demonstrate that the induction of renal calbindin-D28k by $1,25\text{-(OH)}_2\text{D}_3$ is enhanced by high levels of extracellular calcium [12–14]. *In vivo* studies of the receptor-dependent actions of $1,25\text{-(OH)}_2\text{D}_3$ on calbindin-D gene expression have been complicated by the inability to differentiate the effects of hormone deficiency from those of hypocalcemia.

Vitamin D response elements have been found in both the murine calbindin-D9k and calbindin-28k genes [12, 14]; however, Chun Li et al. demonstrated that the VDR dependence of calbindin-D28k gene expression varies among the tissues examined. Consistent with the observation that the kidney and lung express the VDR, calbindin-D28k mRNA levels in these tissues were induced in the control mice treated with $1,25\text{-(OH)}_2\text{D}_3$.

There is evidence in the literature on the effects of vitamin D on bone tissue. As a transcriptional regulator of bone matrix proteins, it induces the expression of osteocalcin and suppresses synthesis of type I collagen. In cell cultures, vitamin D stimulates differentiation of osteoclasts. The crucial effect of vitamin D on bone is to provide the proper balance of calcium and phosphorus to support mineralization [12].

It turns out that vitamin D receptors are present in most if not all cells in the body. Additionally, experiments using cultured cells have demonstrated that vitamin D has potent effects on the growth and differentiation of many types of cells. These findings suggest that vitamin D has

physiologic effects much broader than that of a role in mineral homeostasis and bone function. This is an active area of research and a much better understanding of this area will likely be available in the near future [12].

5. Polymorphisms of the vitamin D receptor

It is known that there exist interindividual differences in the vitamin D endocrine system. This is due to the influence of variations in the DNA sequence of important proteins of this system [14]. For example, different mutations in VDR gene may cause obesity, 1,25-dihydroxyresistant rickets, or cancer [14–16]. The interpretation of VDR polymorphic variations is quite difficult, because the VDR gene is a large one, and the most of these are anonymous restriction fragment length polymorphisms (RFLP) that have unknown functional effect. It is believed that in the population there exist a lot of different mutations, some of them linked with the so-called complex diseases (as osteoporosis), other clinically insignificant or just unexplored [14].

To understand the mechanisms underlying in the associations, it is necessary to study the genomic organization of VDR locus, to determine haplotypes across the gene, and to analyze their relationship with RFLP and finally with a disease.

The VDR gene contains several polymorphisms, including three single nucleotide polymorphisms (SNPs) located near the 3' untranslated region are identified by their restriction endonuclease sites: Apa1 [15, 17], Bsm1 [15, 18], and Taq1 [15, 19]. The Apa1 and the Bsm1 polymorphisms of the VDR gene are considered to be silent single nucleotide polymorphisms and do not change the amino acid sequence of the end-coded protein but can affect gene expression through regulation of mRNA stability [15]. Analyzing the polymorphism of Taq1, it has been shown that depending on the presence or absence of Taq1 restriction site in each allele, products are described as follows: T allele—absence of the restriction site, and t—presence of the restriction site. According to this individuals are classified as TT, Tt, and tt. The TT genotype has been shown to be associated with lower circulating levels of active vitamin D3 [15].

6. The role of vitamin D in the immune system- lymphocytes T and B

There is evidence in the literature that there is an important role for vitamin D (more specifically, calcitriol) in the body's immune system. Most of these researches have been done in cultured cells and in animals with either severe vitamin D deficiency or whose genes have been altered to "knock out" proteins that control vitamin D metabolism or active vitamin D action. Vitamin D receptor is found in significant concentrations in the lymphocyte T and macrophages populations, but the highest concentration is observed in the immature immune cells of the thymus and the mature CD-8 T lymphocytes. This suggests that phagocytes may communicate with T and B cells through calcitriol [20, 21]. When vitamin D is present, it blocks the features of the adaptive immune system that would lead to autoimmunity. Animal studies show that when calcitriol is absent, the cells of the immune system are more likely to attack

the healthy cells of the body (autoimmunity) [20]. There are two ways that vitamin D influences the immunity. First is by avoiding to trigger and arm the T cells during autoimmunity. Vitamin D can stimulate production of transforming growth factor (TGF)- β 1 and interleukin (IL)-4, which may suppress inflammatory T cells activity. Blocking the production of these cells results in diminished ability of T cells to recognize the native protein as foreign. This leads to decrease in killer T cells production [20–22]. In other words, the presence of adequate levels of vitamin D and calcitriol keeps the T cells from attacking the body's own tissues. Second, as the number of T cells decreases, calcitriol also diminishes the role of B cells in producing chemicals to destroy native tissue. What is more, vitamin D inhibits B cell proliferation and blocks its differentiation and immunoglobulin secretion [21–23]. These mechanisms are considered to be involved in triggering/suppressing the autoimmune process in rheumatoid disease, diabetes type I, and systemic lupus erythematosus [21, 22].

The microenvironment in which naive Th cells develop determines which of the two subtypes (Th1 or Th2) will predominate. In normal immune response, both subtypes balance. Th1 produce INF- α , IL-2, and tumor necrosis factor (TNF)- α , and this response is strongly addressed to tumors or intracellular pathogens as viruses [24]. Th2 lymphocytes produce mainly TGF- β 1 and IL-4 and IL-5, and these mediators are linked with extracellular pathogens as bacteria and parasites [24]. It has been proved that Th1 and Th2 are targets of 1,25 (OH) $_2$ D $_3$. 1,25 (OH) $_2$ D $_3$ decreases the production of (IFN- γ), IL-2, and IL-5, and in Th2 cells it increases the production of IL-4 [24, 25]. In conclusion, vitamin D additionally suppresses T cell proliferation and results in shift from a Th1 to a Th2 phenotype [23].

7. The effect of vitamin D on monocytes/macrophages and dendritic cells

In the beginning of the century, several investigators concluded that VDR can be found also on the promyelocytes and that vitamin D can suppress proliferation of promyelocytes and cause their differentiation to monocytes [24]. What is more, it inhibits monocyte production of inflammatory cytokines such as IL-1, IL-6, IL-8, IL-12, and TNF- α [23, 26]. It additionally inhibits dendritic cell (DC) differentiation and maturation, directing to immature phenotype. The inhibition of DC differentiation and maturation plays a crucial role in the developing of the autoimmune processes and self-tolerance to own tissues. When mature DC presents an antigen to a T cell, it directs the immune response against the antigen. In reverse, when the antigen is presented by an immature DC it facilitates tolerance [23]. A decreased concentrations of vitamin D have been reported from different researchers concerning autoimmune diseases as bowel inflammatory disease and diabetes mellitus type I [22–24].

8. Association of allergic sensitization and vitamin D

Epidemiological and laboratory investigations have convincingly shown that vitamin D deficiency is associated with several common diseases, including rickets and other bone

diseases, diabetes, cardiovascular diseases, autoimmune diseases, tuberculosis, and cancer. Sensitization to food allergen is a precursor and a risk factor for the development of allergic diseases later in life, which is why earliest possible detection and modification of risk indicators for food allergen sensitization might prevent the development of allergic diseases [27–29].

Vitamin D deficiency has been proposed as a potential contributing factor in patients with allergic diseases. It has been shown that serum levels of vitamin D correlate with pulmonary function, asthma onset, and the development of allergic diseases. Based on clinical and observational data, the plasma level of 25(OH)D may serve as a “marker” to detect or define a subclinical deficiency of vitamin D [30]. It has recently been demonstrated that lower levels of vitamin D are associated with reduced asthma control. Several studies confirmed that vitamin D interfere favorably with bone turnover as shown by a significant reduction in serum phosphorus of our patients. It is a well-known fact that asthmatic people with lower serum vitamin D concentrations do not respond as well to inhaled glucocorticosteroids therapy as those with optimal vitamin D concentrations. In several studies [31–33], it was proved that supplementation of vitamin D has a beneficial effect on glucocorticosteroids therapy response in patients with severe asthma. A work of Chen Wu et al. in children has supported a role for vitamin D in preventing asthma exacerbations in children in the CAMP trial, especially those children treated with inhaled corticosteroids [34]. Another study found that children with asthma who are deficient in vitamin D levels have less improvement in prebronchodilator FEV1 over the course of 1 year when treated with inhaled corticosteroids as compared with children who are sufficient in vitamin D [35]. These findings support the hypothesis that vitamin D supplementation may enhance the anti-inflammatory function of corticosteroids in patients with asthma, and what is more, we can use vitamin D concentrations as a “marker” concerning the potential effect of treatment in allergic diseases.

Sutherland et al. [36] also found that reduced vitamin D levels are associated with impaired lung function, especially in adults who are not being treated with inhaled corticosteroids. The authors suggested that vitamin D supplementation could be especially beneficial in patients who are not treated with inhaled corticosteroids [36].

9. Vitamin D and atopic dermatitis

The symptoms of atopic dermatitis do not always coincide with the levels of sensitization. To this date, the mechanism of how the vitamin D status is related to the development of atopic dermatitis stays unclear. However, there are two pathophysiological mechanisms in the development of atopic dermatitis: first, immunological mechanisms that influence the Th1/Th2 adaptive immune responses; vitamin D receptor agonists have been shown to impact on Th1 and Th2 cell function, suppress allergen-specific IgE synthesis, inhibit dendritic cell maturation and induce tolerogenic dendritic cells, and finally to induce regulatory CD4⁺CD25⁺25F_{oxp3}⁺T cells. Second, injury of the skin barrier function [26, 29, 31]. Several recent studies have shown that infants with high level of sensitization had a decreased concentration of 25(OH)D levels [27, 29, 37]. What is more, the severity of atopic dermatitis was independently influenced by

the serum 25(OH)D levels and by food allergen sensitization. Promising results of improved eczema symptoms have been found using oral vitamin D supplementation (1000 IU vitamin D for 30 days) in children between 2 and 17 years in two double-blinded placebo-controlled studies performed during wintertime [38, 39].

The prevalence of food allergy has increased dramatically over the past decade and has now reached epidemic levels in countries like Australia or United States, with up to 10% of 12-month-old infants having a clinically confirmed food allergy. As food allergies have increased, vitamin D levels in the population appear to have concurrently decreased. There is no strict evidence in the literature that food allergens could react with vitamin D; however, vitamin D3 supplements have the potential to trigger an allergic reaction in some people, usually when the body mistakenly recognizes the vitamin D3 as a potentially harmful chemical and mounts an immune response against it.

10. Vitamin D and asthma

Maternal vitamin D intake during pregnancy has previously been associated with asthma symptoms in several childhood epidemiological studies [40, 41], while variants in the vitamin D receptor have been associated with asthma in genetic studies [42, 43].

The results of some, but not all, epidemiological studies suggest that vitamin D deficiency is associated with increased risk of wheezing, respiratory tract infections, and asthma symptoms [31–33].

In the past decade of twentieth century there was evidence that there is higher incidence of recurrent respiratory tract infection and nutritional rickets [48, 49]. The evidence that the peak of viral infection is in the winter time when synthesis of vitamin D across the skin is naturally impaired supported that association. In addition, other studies have proved that vitamin D deficiency in pregnant women may result in increased risk of respiratory tract infections in their infants [44–49]. The majority of immune cells express VDRs, mainly after they themselves have been stimulated [40, 41, 48]. The mechanism by which vitamin D regulates inflammation and immunity is complicated. It controls macrophage and dendritic cell activities and various Toll-like receptor mediated events in neutrophils [40, 41], and it diminishes the function of human dendritic cells by decreasing maturation, antigen presentation, and the production of cytokines such as interleukin (IL)-12 and IL-23 [42, 48].

Furthermore, treating macrophages with vitamin D result in the expression of various cytokines and chemokines, including CXCL8, IL-6, and IL-12, and tumor necrosis factor- α [48]. Additionally, vitamin D induces the expression of two antimicrobial peptides—cathelicidin and β -defensin—that are widely expressed in the body and play a key role in innate immunity owing to their chemotactic action and toxin neutralization [48].

The allergic phenotype of asthma is determined by an increased activity of Th2 cells resulting in the production of IgE and inflammatory cytokines causing airway hyperresponsiveness with a predominantly eosinophilic inflammation. Vitamin D would also modulate various

cytokine-induced effects through different cells of the immune system with dose-dependent action. Moderate doses of vitamin D can inhibit the production of both Th1 and Th2 cytokine response, while high concentrations may intensify the Th2 response [49]. Airway inflammation and hyperreactivity are contributed mainly by the regulatory T cells through the production of cytokines such as IL-10 and TGF- β .

What is more, there is evidence in the literature that vitamin D can affect remodeling of the airways in asthma through a direct effect on the proliferation of smooth muscle cells, influence their growth, and contractility [50].

In a study from 2010, it was shown that there exists an association between low levels of vitamin D and impaired lung function, increase of airway hyperresponsiveness, and reduction of glucocorticosteroid response in patients with moderate or severe asthma [51].

Acute lower respiratory tract infections are well-known factor leading to wheezing and asthma-like symptoms. It concerns mainly to bronchiolitis caused by respiratory syncytial virus (RSV). An *in vitro* study has shown that vitamin D can increase the inflammatory response of airway epithelial cells to RSV infection [52], what is more, there is evidence that genetic polymorphisms in VDR are associated with hospitalization due to acute bronchiolitis in infancy [53].

Meta-analysis of randomized controlled trials confirmed the fact that prophylactic supplementation of vitamin D in children significantly reduces the odds of contracting respiratory tract infections [54]. These findings were supported by another study to demonstrate that a higher maternal intake of vitamin D during pregnancy may decrease the recurrent wheeze in early childhood [55]. Additionally, cord blood concentrations of 25(OH)D in neonates correlated with increased risk of lower respiratory tract infections in the first 2 years of life [56].

Vitamin D is also considered to play a big role in allergy and asthma treating as influencing the immunotherapy.

Studies have documented the efficacy and safety of sublingual immunotherapy in pediatric patients with allergies to grass pollen [57–60]. However, an important issue in mucosal immunotherapy is how to improve efficacy. There are a few studies on assessing modification of the effectiveness of sublingual immunotherapy in children. In two studies from Poland [32, 33] reduction in combined symptom-medication score, nasal symptoms in children receiving vitamin D supplementation to SLIT was observed compared to those receiving SLIT and placebo, as well as lower asthma symptoms.

Up to this date, there is evidence in the literature that vitamin D supplementation has a beneficial effect on allergy treatment. It has been proved that vitamin D supplementation in patients with allergic rhinitis treated with SLIT results in overall clinical improvement; however, vitamin D supplementation is more effective in the reduction of nasal and asthma symptoms and improvement in symptoms observed during SLIT were fairly clearly correlated with the serum level of vitamin D [31]. In a different study of Stelmach et al., it was shown that clinical and immunological efficacy of allergen-specific immunotherapy in children with asthma allergic to house dust mites was correlated with 25(OH)D serum concentration [32].

Another study of Stelmach et al. demonstrated that combined administration of a systemic corticosteroid and allergen extract suppressed early clinical and immunological effects of SIT and that vitamin D₃ prevented this “adverse” effect of corticosteroids. Therefore, a favorable effect of vitamin D in immunotherapy is very encouraging [31]. Since there is an evidence that the efficacy of allergen-specific immunotherapy correlates with 25(OH)D serum concentration, it seems to be reasonable to monitor the serum level of 25(OH)D in children undergoing allergen immunotherapy, especially in those at risk of vitamin D insufficiency. It seems that the serum level of 25(OH)D above 30 ng/mL facilitates the optimal effect of allergen immunotherapy. In a study of Stelmach et al. [31–33], administration of 1000 IU vitamin D once daily with SLIT significantly reduced phosphorus in serum of children, which suggests its beneficial effect on calcium-phosphorus metabolism and on collagen turnover in children. Therefore, the clinical implication of that study suggests that the supplementation of SLIT with vitamin D should be recommended for treatment of allergic rhinitis in children.

11. Recommendations

In different countries there exist different recommendations concerning vitamin D supplementation. Currently, European Food Safety Authority (EFSA) proposed a daily intake of 100 mcg (equal to 400 IU) vitamin D for adults including pregnant and breastfeeding women, 50 mcg for children 11–17 years, and 25 mcg for infants [61, 62]. The institute of Medicines Committee in its report from 2011 recommended at least 600 IU for infants with maximum upper limit of 2500 IU for children 1–3 years and 3000 IU for children 4–8 years and 4000 IU for 9 years and older [61]. By this date, it is common practice for all physicians to supplement vitamin D under the verification of 25(OH)D concentration. The last recommendations for vitamin D supplementation in Central Europe state that 30–50 ng/mL are considered as optimal [62].

Based on its review of data of vitamin D needs, a committee of the Institute of Medicine concluded that persons are at risk of vitamin D deficiency at serum 25(OH)D concentrations <30 nmol/L (<12 ng/mL). Some are potentially at risk for inadequacy at levels ranging from 30 to 50 nmol/L (12–20 ng/mL). Practically, all people are sufficient at levels ≥50 nmol/L (≥20 ng/mL); the committee stated that 50 nmol/L is the serum 25(OH)D level that covers the needs of 97.5% of the population. Serum concentrations >125 nmol/L (>50 ng/mL) are associated with potential adverse effects [63].

Intake reference values for vitamin D and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine of The National Academies (formerly National Academy of Sciences) [63].

The FNB established an RDA for vitamin D representing a daily intake that is sufficient to maintain bone health and normal calcium metabolism in healthy people. RDAs for vitamin D are listed in both International Units (IUs) and micrograms (mcg); the biological activity of 40 IU is equal to 1 mcg (**Table 1**). Even though sunlight may be a major source of vitamin D for some, the vitamin D RDAs are set on the basis of minimal sun exposure [63].

| 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) | | |

*Adequate intake (AI).

Table 1. Recommended dietary allowances (RDAs) for vitamin D [63].

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