Review paper

Vitamin D impact on immune functions: implications for preventive strategy of allergic disease?

Aleksandra Szczawińska-Popłonyk, Anna Bręborowicz

Department of Paediatric Pneumonology, Allergology and Clinical Immunology, III Chair of Pediatrics, Poznan University of Medical Sciences, Poland
Head: Prof. Anna Bręborowicz MD, PhD

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Abstract

Asthma and allergic diseases are substantial global health problems with a higher prevalence in the westernized countries. It has been proposed that vitamin D deficiency resulting from reduced exposure to sunlight and changes in lifestyle as well as dietary habits may contribute to a high prevalence of asthma and allergic diseases. This review examines the scientific evidence for pluripotent immunoregulatory actions of vitamin D in conjunction with nuclear actions as well as genetic and epigenetic determinants of the vitamin D effects. Findings of epidemiological and clinical studies on the potential association between vitamin D and allergic disease and asthma are reviewed.

Key words: vitamin D, immunity, asthma, allergy, children.

Introduction

Beyond its well-known effects on calcium homeostasis and bone mineralization, vitamin D has become recently recognized as a pluripotent immunoregulator of biological functions with a particular role in immune tolerance and antimicrobial immunity. Although extensive research has been carried out on the vitamin D action, its molecular and cellular mechanisms have not been fully elucidated thus far.

Humans obtain vitamin D in two different forms as prohormones, namely as cholecalciferol or vitamin D_3, a product of the photochemical reaction in keratinocytes from 7-dehydrocholesterol by exposure to sunlight as well as ergosterol or vitamin D_2, synthesized in plants exposed to UVB radiation. The former mechanism provides 80% of vitamin D to the human organism, although both cholecalciferol and ergosterol may also be obtained from animal and plant dietary products, respectively [1]. In the circulation, the precursor is complexed with the vitamin D-binding protein (VDBP) and transported to the liver where the first step of hydroxylation occurs by the mitochondrial cytochrome P-450 25-hydroxylase enzymes encoded by *CYP27A1* and/or *CYP2R1* genes giving rise to $25(OH)D_3$. Subsequent renal hydroxylation at the 1α position by the cytochrome P450 enzyme encoded by *CYP27B1* gene leads to the generation of the bioactive 1α,25-dihydroxyvitamin D ($1,25(OH)_2D_3$) [2]. The proximal kidney tubule is admittedly the primary place of the latter process, however many cell types, including monocytes/macrophages, dendritic cells and lung epithelial cells are capable of synthesizing $1,25(OH)_2D_3$ [3-5]. These data in conjunction with expression of the vitamin D receptor (VDR) in many immune cells have led to the recognition of the associations between the vitamin D metabolism and chronic autoimmune, infectious, allergic, cardiovascular, neoplastic, and neurodegenerative disorders [6, 7].

The determinants of the vitamin status include exposure to the sunlight and time spent outdoors, diet rich in natural and fortified vitamin D-rich products and use of supplements, season of the year, latitude, atmospheric conditions, age, skin pigmentation as well as coverage with garments and the use of sunblocks. As both children and adults spend on average only 10% of daylight hours outside [8], the westernized lifestyle poses a high risk of vitamin D deficiency and increased incidence of related diseases.

Defining the vitamin D status

The major circulating form of vitamin D is $25(OH)D_3$, an inactive, relatively stable metabolite that has a half-life of approximately 2-3 weeks and most closely reflects vitamin D classical physiology and its supply to the organ-

Address for correspondence: Aleksandra Szczawińska-Popłonyk MD, PhD, Department of Paediatric Pneumonology, Allergology and Clinical Immunology, Poznan University of Medical Sciences, 27/33 Szpitalna, 60-572 Poznan, Poland, phone/fax: +48 61 848 01 11, e-mail: ola@malwa.com.pl, klinikapad@xmail.sk5.am.poznan.pl

ism [9]. Therefore, 25(OH)D_3 is the most appropriate biochemical marker used for determination of the vitamin D status. Serum 25(OH)D_3 concentrations of 10 ng/ml (25 nmol/l) have been for long considered to be the cut-off lower limit of its adequate level in terms of maintaining parathyroid hormone homeostasis and preventing rickets. Despite lack of the absolute consensus regarding the normal range of 25(OH)D_3, the currently recommended level by most authors for both children and adults is > 30 ng/ml [10, 11], and even levels ranging from 50 ng/ml to 80 ng/ml are considered to be optimal with regard to possible health complications beyond rickets [12]. 25(OH)D_3 levels that fall between 20 ng/ml and 30 ng/ml are considered insufficient and levels below 20 ng/ml are recognized as vitamin D deficiency. However, these biochemical definitions of the vitamin D status, based mainly on hormonal and metabolic studies in adults, may not be physiologically optimal for the pediatric population and may implicate the risk of chronic disorders later throughout the lifespan.

The prevalence of inadequate (< 20 ng/ml or 50 nmol/l) vitamin D status in children and adolescents is currently a matter of concern since in Europe and in the USA it has been estimated to occur in 46-73% of the population during winter months [13-15] and 24-29% in the summer [13, 15]. In Poland, changes in dietary habits and physical activity levels in children and adults as well as weather conditions enabling effective skin synthesis of vitamin D from April to September have led to a continuously increasing prevalence of vitamin D insufficiency and the need to recommend its prophylactic supplementation in different age groups, which was reviewed by Charzewska *et al*. [16, 17] and Dobrzanska *et al*. [18].

Molecular level of the vitamin D activity

The vitamin D receptor, encoded by the *VDR* gene, belongs to the nuclear hormone receptor superfamily and NR1I subgroup [19]. The VDR mediates its action by first binding the ligand, 1α,25(OH)$_2$$D_3$, and then forming a heterodimer with the retinoid X receptor (RXR), which in turn binds to the vitamin D-responsive elements (VDREs) in the promoter regions of relevant target genes and either initiates recruitment of transcriptional complexes with nuclear proteins or downregulates transcription [20]. The VDR expression that has been identified in different cell types of all tissues in the human body and the regulation of approximately 3% of the human genome via the vitamin D pathway reflect its important role in biological processes [21].

The non-classical immunomodulatory actions attributed to vitamin D are warranted by the VDR expression in immune cells – macrophages and their monocyte precursors, dendritic cells as well as T and B lymph cells. The initial observation of the 1α-hydroxylase activity and the ability of macrophages to produce 1,25(OH)$_2$$D_3$ upon stimulation with interferon gamma along with the endogenous VDR expression suggest both autocrine and intracrine mechanisms of the vitamin D action in these cells [22]. Subsequently, it was demonstrated that the vitamin D response elements are present in the promoter regions of *CAMP* (also known as hCAP18/LL-37/FALL37) and *DEFB4* genes encoding for the antimicrobial peptides (AMPs), cathelicidin and β-defensin 2, respectively [23, 24]. The ability to promote the synthesis of cathelicidin upon the macrophage Toll-like receptor (TLR) 1/2 activation by microbial PAMPs (pathogen-associated molecular patterns) is the most likely mechanism by which vitamin D interacts with the innate immune response. It is worth noting that regulation of antimicrobial peptides by 1,25(OH)$_2$$D_3$ has been shown in a variety of cells other than macrophages, such as keratinocytes [25, 26], lung epithelial cells [27, 28], and myeloid cell lines [29], thereby priming these cells for the innate immune response to pathogens.

In dendritic cells, 1,25(OH)$_2$$D_3$ regulates their maturation as well as impacts the phenotype and function of these cells. Preferentially, myeloid dendritic cells (mDC), which are effective antigen presenting cells, are athe target of the vitamin D regulatory actions, leading to the increase of their tolerogenicity, whereas protolerogenic plasmacytoid dendritic cells (pDC) are less affected [30]. A key mechanism of this vitamin D pathway-related immunomodulation relies on downregulating expression of the costimulatory molecules, such as CD40, CD80, and CD86 as well as cytokine IL-12 along with upregulating cytokine IL-10. In myeloid DCs, 1,25(OH)$_2$$D_3$ inhibits intracellular signaling by nuclear factor-κB (NF-κB) pathway and regulates the T cell response, promoting generation of inducible Foxp3+ regulatory T cells at the periphery [31].

The VDR expression in the resting T cells is almost undetectable, but increases during their proliferation upon antigenic stimulation, resulting in vitamin D-dependent modulation of the T lymphocyte phenotype and shaping the cellular immune response. Downregulation of antigen-specific interferon γ (IFN-γ) and interleukin 17 (IL-17) responses in T lymph cells [32], resulting in predominating Th2-type immune processes may be a direct effect of 1,25(OH)$_2$$D_3$ on VDR expressing T lymphocytes or an indirect action via DCs in a paracrine fashion [33].

In the activated B cell, vitamin D exerts an inhibitory effect on development and functions, decreasing plasma cell differentiation and immunoglobulin production, contributing to B lymphocyte homeostasis [34, 35]. Detailed vitamin D effects on immune cells are displayed in Figure 1.

Genetic polymorphisms and epigenetic interactions in the pathogenesis of allergic diseases

There is growing evidence that diverse sensitivity to, and effects of the vitamin D actions may be due to genetic variability of the vitamin D pathway influencing activ-

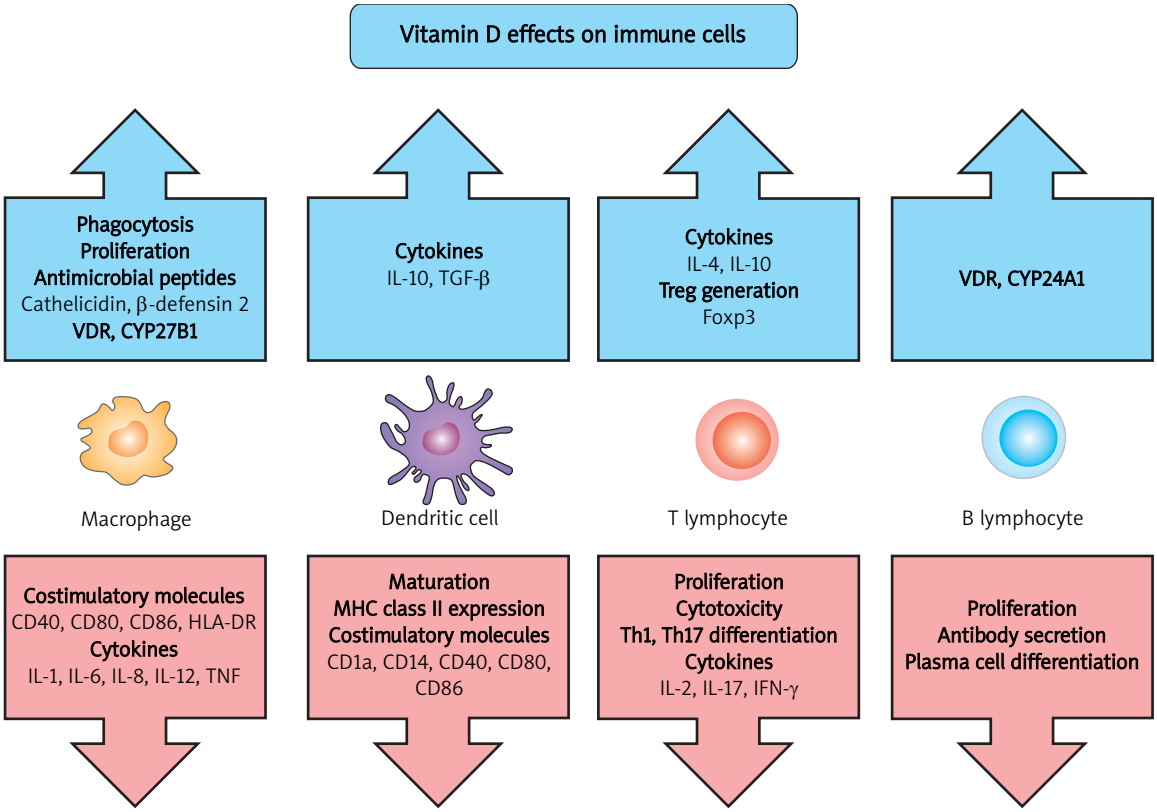

Figure 1. Vitamin D effects on immune cells

ity of a wide number of related genes either directly or indirectly by epigenetic, gene-environmental interactions. Single nucleotide polymorphisms (SNPs) are genetic variants frequently occurring in the population and showing a functional impact on the immune system and contributing to the susceptibility to immune-mediated diseases. So far, three adjacent restriction fragment length polymorphisms for BsmI, ApaI, and TaqI at the 3' end of the *VDR* gene have been most frequently studied [21].

Since the VDR is found in many different cell types, including immune cells, and mediates vitamin D-dependent effects on immune regulation by altering the differentiation and proliferation response, polymorphism of the *VDR* gene may be associated with intersubjectpredisposition to allergic diseases. Furthermore, *VDR* maps to the centromeric region on the long arm of the chromosome 12, that has been linked to asthma and allergy-related phenotypes in genome-wide linkage analysis [36, 37]. Several polymorphisms of the *VDR* gene have been identified, which may be relevant to asthma and atopy. It is worth noting that FokI polymorphism was demonstrated to have a major impact on the immune system, resulting in *VDR* proteins with different structures and functional consequences in immune cells. The presence of the shorter F-VDR was associated with higher NF-κB and IL-12p40-driven transcription and more active inflammatory response [38]. In the Canadian asthma family-based cohort, an increased risk of asthma was shown to be associated with the ApaI C allele of the *VDR* gene [39].

Due to the fact that numerous metabolic pathways may play a major role in complex multifactorial diseases, polymorphism in other genes involved in vitamin D system may be associated with asthma and atopy. In the German Asthma Family Study, Wjst *et al.* [40] identified SNPs in the *IL-10*, *VDBP*, *CYP2R1* and *CYP24A1* genes associated with asthma and IgE levels. Furthermore, a modest association with asthma or atopy was also confirmed in the study by Bossé *et al.* [41] with regard to SNPs in the *IL-10* and *CYP24A1* genes. In that report, the authors paid special attention to the fact that both single nucleotide polymorphisms as well as orientation of the risk alleles may differ between populations and the genetic effect of the VDR pathway may be overruled by other immune processes and be detectable in specific environments or age-related context.

Gene-environmental interactions, particularly these environmental exposures that act early in the postnatal period, as stated in the Barker's hypothesis, may epige-

netically contribute to prominent modifications of the vitamin D and VDR pathways [42]. Environmental stresses may lead to modifications in histone proteins and associated regions of DNA by binding specific factors that alter the structural property of chromatin. In particular, histone modifications by a variety of enzymes, such as acetyltransferases, deacetylases, protein kinases, methyltransferases, demethylases, and ubiquitination enzymes influence the activation or repression of gene expression for various inflammatory mediators. Thus, specific epigenetic modifications of vitamin D and VDR pathways may significantly contribute to the specific disease phenotype [43].

Vitamin D status and the risk of allergic diseases

The vitamin D effects on the immune phenomena have been translated into implications regarding the relationship between the vitamin D status and the risk of allergic diseases. The impact of $1,25(OH)_2D_3$ on the fetal lung growth and development as well as surfactant production in alveolar type II cells [44] in conjunction with the effect on the developing immune system and promotion of the protolerogenic phenotype leads to questions about the role of vitamin D in the development of asthma.

Several studies showed a positive correlation between either the maternal serum $25(OH)D_3$ during pregnancy or the higher vitamin D intake as well as the reduced risk of respiratory tract infections and early childhood wheezing in the offspring [45-47], the effect that might be owing both to the immunoregulatory activity of vitamin D and also to its antiviral actions [48]. Furthermore, in a study by Miyake *et al.* [49], the protective effect of maternal diary food and vitamin D intake during pregnancy was not exclusively confined to respiratory symptoms, but the reduced risk of eczema in infants was also demonstrated.

However, it is worth noting that there is a considerable inconsistency regarding the results of the observational studies, notably because of influence of possible confounders. Morales *et al*. [50] admittedly showed the association between the higher maternal $25(OH)D_3$ concentrations in pregnancy and the lower risk of respiratory tract infections, but not of wheezing and asthma in childhood. Moreover, contrary arguments that vitamin D excess may increase the risk of allergic diseases have also been proposed, based on the independent reports by Gale *et al*. [51] and Rothers *et al*. [52].

Another group of clinical studies was aimed at the assessment of the relationship between vitamin D status and allergic disease severity. The first epidemiological study demonstrating an association between low vitamin D levels and increased markers of asthma severity, including serum IgE, eosinophil count, the use of inhaled corticosteroids and hospitalization rate in the previous year was conducted among schoolchildren in Costa Rica [53]. Subsequently, higher odds of severe asthma exacerbations were shown by the same group of researchers in the Childhood Asthma Management Program Study in North American children [54]. In a study by Gupta *et al*. [55], the link between lower vitamin D levels with not only clinical manifestations but also with the decreased spirometric parameters as well as with histological features of the airway remodeling in children with severe, therapy-resistant asthma was demonstrated. This mechanistic approach to the relationships between serum vitamin D levels and asthma severity assessed based on the pulmonary function test was also reported by Alyasin *et al*. [56] and Tolppanen *et al*. [57], showing a positive correlation between $25(OH)D_3$ status and the lung function.

The role of vitamin D as a possible preventive measure for asthma was explored in the study by Majak *et al*. [58]. The authors demonstrated that vitamin D supplementation during a period from September to July prevented decline of serum $25(OH)D_3$, the effect that was associated with a reduced risk of asthma exacerbations triggered by acute respiratory tract infections. Assessment of the impact of vitamin D on atopic dermatitis as a possible therapeutic intervention was also investigated. A significant improvement in baseline score was noted in children receiving vitamin D supplementation, however, because of the small sample size comprising 5 patients, further trials on the effect of vitamin D on this entity are indispensable [59]. With a global increase in food allergy, the role of vitamin D supplementation and food allergy outcomes is a priority area of future research.

Concluding remarks

Given the potential for vitamin D to suppress inflammatory responses and enhance the antimicrobial pathway activity, it has been suggested that its deficiency might be blamed for the epidemic of allergic diseases. Therefore, the question whether implications regarding the adequate status of vitamin D as preventive strategy and treatment modality for asthma and other allergic disorders are being admitted as an endpoint of the aforementioned considerations, remains unanswered and requires further clinical controlled prospective studies.

References

1. O'Mahony L, Stepien M, Gibney MJ, et al. The potential role of vitamin D enhanced foods in improving vitamin D status. Nutrients 2011; 3: 1023-41.
2. Herr C, Greulich T, Koczulla RA, et al. The role of vitamin D in pulmonary disease: COPD, asthma, infection, and cancer. Respir Res 2011; 12: 31.
3. Hewison M. Vitamin D and the intracrinology of innate immunity. Mol Cell Endocrinol 2010; 321: 103-11.
4. Penna G, Adorini L. 1 Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. J Immunol 2000; 164: 2405-11.

5. Hansdottir S, Monick MM, Hinde SL, et al. Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. J Immunol 2008; 181: 7090-9.
6. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004; 80 (6 Suppl): 1678S-88S.
7. Kulie T, Groff A, Redmer J, et al. Vitamin D: an evidence-based review. J Am Board Fam Med 2009; 22: 698-706.
8. Engelsen O. The relationship between ultraviolet radiation exposure and vitamin D status. Nutrients 2010; 2: 482-95.
9. Holick MF. Vitamin D status: measurement, interpretation, and clinical application. Ann Epidemiol 2009; 19: 73-8.
10. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357: 266-81.
11. Bischoff-Ferrari HA, Giovannucci E, Willett WC, et al. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 2006; 84: 18-28.
12. Cashman KD. Vitamin D in childhood and adolescence. Postgrad Med J 2007; 83: 230-5.
13. Kull M Jr, Kallikorm R, Tamm A, Lember M. Seasonal variance of 25-(OH) vitamin D in the general population of Estonia, a Northern European country. BMC Public Health 2009; 9: 22.
14. Cheng S, Tylavsky F, Kröger H, et al. Association of low 25-hydroxyvitamin D concentrations with elevated parathyroid hormone concentrations and low cortical bone density in early pubertal and prepubertal Finnish girls. Am J Clin Nutr 2003; 78: 485-92.
15. Gordon CM, DePeter KC, Feldman HA, et al. Prevalence of vitamin D deficiency among healthy adolescents. Arch Pediatr Adolesc Med 2004; 158: 531-7.
16. Charzewska J, Chlebna-Sokół D, Chybicka A, et al. Recommendations of prophylaxis of vitamin D deficiency in Poland (2009). Med Wieku Rozwoj 2010; 14: 218-23.
17. Charzewska J, Chlebna-Sokół D, Chybicka A, et al. Prophylaxis of vitamin D deficiency-Polish recommendation 2009. Ginekol Pol 2010; 81: 149-53.
18. Dobrzańska A, Charzewska J, Chlebna-Sokół D, et al. Prophylaxis of vitamin D deficiency-Polish recommendations 2009. Pol Merkur Lekarski 2010; 28: 130-3.
19. Rochel N, Moras D. Ligand binding domain of vitamin D receptors. Curr Top Med Chem 2006; 6: 1229-41.
20. Valdivielso JM, Fernandez E. Vitamin D receptor polymorphisms and diseases. Clin Chim Acta 2006; 371: 1-12.
21. Uitterlinden AG, Fang Y, Van Meurs JB, et al. Genetics and biology of vitamin D receptor polymorphisms. Gene 2004; 338: 143-56.
22. Hewison M. Vitamin D and the immune system: new perspectives on an old theme. Endocrinol Metab Clin North Am 2010; 39: 365-79.
23. Wang TT, Nestel FP, Bourdeau V, et al. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J Immunol 2004; 173: 2909-12.
24. Hiemstra PS. The role of epithelial beta-defensins and cathelicidins in host defense of the lung. Exp Lung Res 2007; 33: 537-42.
25. Dombrowski Y, Peric M, Koglin S, et al. Control of cutaneous antimicrobial peptides by vitamin D3. Arch Dermatol Res 2010; 302: 401-8.
26. Schauber J, Gallo RL. Antimicrobial peptides and the skin immune defense system. J Allergy Clin Immunol 2009; 124 (3 Suppl 2): R13-8.
27. Hansdottir S, Monick MM, Hinde SL, et al. Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. J Immunol 2008; 181: 7090-9.
28. Tecle T, Tripathi S, Hartshorn KL. Defensins and cathelicidins in lung immunity. Innate Immun 2010; 16: 151-9.
29. Sørensen O, Arnljots K, Cowland JB, et al. The human antibacterial cathelicidin, hCAP-18, is synthesized in myelocytes and metamyelocytes and localized to specific granules in neutrophils. Blood 1997; 90: 2796-803.
30. Adorini L, Penna G. Dendritic cell tolerogenicity: a key mechanism in immunomodulation by vitamin D receptor agonists. Hum Immunol 2009; 70: 345-52.
31. Kushwah R, Hu J. Role of dendritic cells in the induction of regulatory T cells. Cell Biosci 2011; 1: 20.
32. Joshi S, Pantalena LC, Liu XK, et al. 1,25-dihydroxyvitamin D(3) ameliorates Th17 autoimmunity via transcriptional modulation of interleukin-17A. Mol Cell Biol 2011; 31: 3653-69.
33. Nelson CD, Nonnecke BJ, Reinhardt TA, et al. Regulation of Mycobacterium-specific mononuclear cell responses by 25-hydroxyvitamin D3. PLoS One 2011; 6: e21674.
34. Chen S, Sims GP, Chen XX, et al. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. J Immunol 2007; 179: 1634-47.
35. Adams JS, Hewison M. Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. Nat Clin Pract Endocrinol Metab 2008; 4: 80-90.
36. Raby BA, Silverman EK, Lazarus R, et al. Chromosome 12q harbors multiple genetic loci related to asthma and asthma-related phenotypes. Hum Mol Genet 2003; 12: 1973-9.
37. Raby BA, Lazarus R, Silverman EK, et al. Association of vitamin D receptor gene polymorphisms with childhood and adult asthma. Am J Respir Crit Care Med 2004; 170: 1057-65.
38. van Etten E, Verlinden L, Giulietti A, et al. The vitamin D receptor gene FokI polymorphism: functional impact on the immune system. Eur J Immunol 2007; 37: 395-405.
39. Poon AH, Laprise C, Lemire M, et al. Association of vitamin D receptor genetic variants with susceptibility to asthma and atopy. Am J Respir Crit Care Med 2004; 170: 967-73.
40. Wjst M, Altmüller J, Faus-Kessler T, et al. Asthma families show transmission disequilibrium of gene variants in the vitamin D metabolism and signalling pathway. Respir Res 2006; 7: 60.
41. Bossé Y, Lemire M, Poon AH, et al. Asthma and genes encoding components of the vitamin D pathway. Respir Res 2009; 10: 98.
42. Tantisira KG, Weiss ST. Childhood infections and asthma: at the crossroads of the hygiene and Barker hypotheses. Respir Res 2001; 2: 324-7.
43. Sundar IK, Rahman I. Vitamin d and susceptibility of chronic lung diseases: role of epigenetics. Front Pharmacol 2011; 2: 50.
44. Rehan VK, Torday JS, Peleg S, et al. 1Alpha,25-dihydroxy-3-epi-vitamin D3, a natural metabolite of 1alpha,25-dihydroxy vitamin D3: production and biological activity studies in pulmonary alveolar type II cells. Mol Genet Metab 2002; 76: 46-56.
45. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. Am J Clin Nutr 2007; 85: 788-95.
46. Devereux G, Litonjua AA, Turner SW, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. Am J Clin Nutr 2007; 85: 853-9.

47. Camargo CA Jr, Ingham T, Wickens K, et al. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. Pediatrics 2011; 127: e180-7.
48. Mansbach JM, Camargo CA Jr. Respiratory viruses in bronchiolitis and their link to recurrent wheezing and asthma. Clin Lab Med 2009; 29: 741-55.
49. Miyake Y, Sasaki S, Tanaka K, Hirota Y. Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants. Eur Respir J 2010; 35: 1228-34.
50. Morales E, Romieu I, Guerra S, et al. Maternal vitamin D status in pregnancy and risk of lower respiratory tract infections, wheezing, and asthma in offspring. Epidemiology 2012; 23: 64-71.
51. Gale CR, Robinson SM, Harvey NC, et al. Maternal vitamin D status during pregnancy and child outcomes. Eur J Clin Nutr 2008; 62: 68-77.
52. Rothers J, Wright AL, Stern DA, et al. Cord blood 25-hydroxyvitamin D levels are associated with aeroallergen sensitization in children from Tucson, Arizona. J Allergy Clin Immunol 2011; 128: 1093-9.
53. Brehm JM, Celedón JC, Soto-Quiros ME, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. Am J Respir Crit Care Med 2009; 179: 765-71.
54. Brehm JM, Schuemann B, Fuhlbrigge AL, et al. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. J Allergy Clin Immunol 2010; 126: 52-8.
55. Gupta A, Sjoukes A, Richards D, et al. Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. Am J Respir Crit Care Med 2011; 184: 1342-9.
56. Alyasin S, Momen T, Kashef S, et al. The relationship between serum 25 hydroxy vitamin D levels and asthma in children. Allergy Asthma Immunol Res 2011; 3: 251-5.
57. Tolppanen AM, Williams D, Henderson J, et al. Serum 25-hydroxy-vitamin D and ionised calcium in relation to lung function and allergen skin tests. Eur J Clin Nutr 2011; 65: 493-500.
58. Majak P, Olszowiec-Chlebna M, Smejda K, Stelmach I. Vitamin D supplementation in children May prezent astma exacerbation triggered by acute respiratory infection. J Allergy Clin Immunol 2011; 127: 1294-6.
59. Sidbury R, Sullivan AF, Thadhani RI, Camargo CA Jr. Randomized controlled trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: a pilot study. Br J Dermatol 2008; 159: 245-7.