

Is vitamin D deficiency correlated with childhood wheezing and asthma ?

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1. ABSTRACT

There is increasing evidence that vitamin D regulates immune responses. There is also epidemiological evidence of a relationship between vitamin D deficiency and development of asthma. In addition, several epidemiological studies suggest that low levels of vitamin D during pregnancy and early life are inversely associated with the risk of developing respiratory infections and wheezing in childhood. Vitamin D also seems to reduce asthma exacerbation and increase the response to glucocorticoids. These findings have led to considering a possible link between the occurrence of allergic respiratory diseases and low levels of vitamin D. However, the precise role of vitamin D in the pathogenesis of asthma still remains unclear, emphasizing the need for well-designed trials on vitamin D supplementation to decipher its role in preventing and/or managing the disease. This review examines the relationship that exists between vitamin D deficiency and childhood wheezing and asthma.

2. INTRODUCTION

Vitamin D (VD) is an essential nutrient mainly acquired through endogenous synthesis in the skin after exposure to sunlight, and in a lesser percentage through the diet and dietary supplements (1). Within the body VD acts as a hormone and it is well recognized for its role in calcium and phosphorus homeostasis, bone mineralization and skeletal health (1,2). The recent identification of VD receptors in most tissues and cells in the human body, including cells of the immune system, combined with the demonstration that several cells in the body are capable of converting the primary circulating form of VD, 25-hydroxyvitamin D [25(OH)D], to the active form 1,25-dihydroxyvitamin D [1,25(OH)₂D], has exponentially increased interest in the extra-skeletal effects of this hormone (1-3).

Emerging evidence has shown that VD deficiency (VDD) plays a role in several chronic illnesses,

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including various cancers, autoimmune disorders, cardiovascular diseases, respiratory diseases and infections (1,4). Moreover, recent attention has focused on the possible relationship between VDD and the pathogenesis of allergic diseases (5,6). Whereas there is a lack of consistent data addressing the topic of VD supplementation in the prevention of food allergies (7), several epidemiological studies have reported significant associations between VDD and increased risk of childhood wheezing and asthma exacerbation (8). However, the precise role of VD in the immune system and in allergic respiratory diseases still remains to be clearly defined (9,10).

This paper reviews current data regarding the relationship between VDD and childhood wheezing and asthma and emphasizes the need for well-designed, prospective trials on VD supplementation necessary to decipher its role in the prevention and/or future management of asthma and its morbidity.

3. VITAMIN D DEFICIENCY: AN UNDER-RECOGNIZED PROBLEM

In recent years there has been evidence of worldwide VDD at all ages, even in countries with apparent adequate exposure to sunlight and dietary supplements (11,12). This could be attributed to a combination of modified eating habits, e.g. less consumption of fish liver oil, fish, milk, eggs and margarine, which are natural sources of VD; behavioural habits, e.g. less time spent outdoors, less exposure to sunlight, clothing coverage for personal or religious reasons; and national campaigns such as the promoted use of sunscreen to prevent skin cancer. Furthermore, other intrinsic factors may affect individual VD status such as age, gender, skin pigmentation (the melanin content of the skin may interfere with VD synthesis), obesity (the adipose tissue takes up VD, which is a fat-soluble vitamin) (13), and intensity of exposure to sunlight, which is influenced both by seasons (it is lower in winter and higher in summer) and by latitude (it decreases with distance from the equator) (11,12).

On the basis of these premises, VDD is an under-recognized on-going epidemic, not only in the elderly, but also in pregnant/breastfeeding women and in their offspring (14,15). The measurement of 25(OH)D serum levels, which is the main circulating VD metabolite with the most potent biological effects, is considered the best indicator of VD status, reflecting total VD intake from sunlight exposure, supplementation and diet (16). Although there is no scientific consensus on optimal VD serum levels for global health and on doses to be recommended for its supplementation, several experts agree on defining VDD as a 25(OH)D serum concentration of less than 20 ng/ml (< 50 nmol/L) and VD insufficiency as a 25(OH)D serum level between 21 and 29 ng/ml (50–70 nmol/L) (17,18).

4. THE VITAMIN D HYPOTHESIS IN THE PATHOGENESIS OF ALLERGIC RESPIRATORY DISEASES

There is plenty of evidence to show that there has been an increased frequency in asthma and allergic diseases

worldwide over the past few decades, with the industrialized countries furthest away from the equator reporting the highest prevalence. The recent discovery of a parallel epidemiological pattern between the asthma epidemic and VDD (both conditions have been associated with obesity, African-American ethnicity and Western country lifestyles), along with demonstrations that VD regulates immune responses, have led to a hypothesis of a causal relationship between the low VD on-going epidemic and the burden of allergic respiratory diseases (19-21).

To date, there are several lines of evidence demonstrating that VD has complex immunomodulatory properties for both innate and adaptive immune system functions, aside from its well-recognized role in calcium/phosphorus homeostasis and bone physiology (22). Most cells of the immune system, including B- and T-lymphocytes, macrophages and antigen-presenting cells, have been shown to express the VD receptor, which is the mediator of VD action (23,24). Furthermore, all these immune cells express the enzyme 1 α -hydroxylase, which converts the circulating pro-hormone 25(OH)D into the active form 1,25(OH)₂D. In its active form, VD has been shown to contribute to innate immunity by enhancing the expression of genes encoding for antimicrobial peptides, such as cathelicidin (25,26). Monocytes and macrophages exposed to a lipopolysaccharide or to mycobacterium tuberculosis have been seen to up-regulate both the VD receptor and the 1 α -hydroxylase genes. This up-regulation increases the synthesis of 1,25(OH)₂D and cathelicidin, which is central in innate immune response against respiratory tract pathogens (25). There is also evidence that 1,25(OH)₂D maintains mucosal integrity and reinforces the physical epithelial barrier against bacteria by stimulating junction genes (27). In addition, VD has been shown to impact the Th1/Th2 balance of the adaptive immune response, inhibit Th1-cytokines synthesis, suppress maturation and antigen presenting capability of dendritic cells, suppress allergen-specific IgE synthesis and finally to enhance expression of CD4+CD25+Foxp3+ T- regulatory cells (28-30). In vitro studies confirmed that exposure to 1,25(OH)₂D converts human CD4+ T-cells into IL-10 secreting T-regulatory cells and suppresses antibody production by human B-cells, with further elaboration of tolerizing and anti-inflammatory cytokines (31,32).

Several mechanisms suggest that VDD could contribute to the development of childhood wheezing and asthma (33). Both animal models and studies in human fetal tissues showed that VD is implicated in fetal lung growth and maturation (34-36). There is also evidence of a role of VD in maintaining lung structure and pulmonary function (37,38). The active form 1,25(OH)₂D has been seen to decrease lung inflammation and airway hyper-responsiveness by inhibiting synthesis and releasing inflammatory cytokines from bronchial smooth muscle cells (such as RANTES and matrix metalloproteinases), as well as promoting T-regulatory cell activity (39-41). Moreover, two recent family-based studies have reported an association between VD receptor variants and the presence of asthma and atopy (42,43). However, these findings were not confirmed by two other studies (44,45).

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Emerging evidence indicates that VD is protective against respiratory-tract infections (5,46), which are the most common triggering factors of childhood wheezing and asthma exacerbation (47). Finally, VD has been shown to affect expression of several genes in human bronchial smooth muscle cells, including genes involved in smooth muscle cell growth, proliferation and morphogenesis (48,49). This also suggests a possible involvement of VD in airway remodeling, which may be important for future prevention and/or treatment of asthma and asthma morbidity (50).

5. VITAMIN D DEFICIENCY AND CHILDHOOD WHEEZING

Wheezing is a very common respiratory symptom during childhood. Epidemiological studies have reported that almost one-third of all children wheeze at least once in the first three years of life, with nearly 50% of all children having at least one wheezing episode by the age of 6 years (51-53). However, early childhood wheezing is a heterogeneous condition, which has several phenotypic expressions and a complex relationship with the development of asthma later in life (54). Despite the fact that recurrent wheezing is one of the major symptoms of asthma and that asthmatics are more likely than other children to wheeze in childhood, the majority of children who wheeze in early life will have a resolution of the symptom by the age of 3 years, or 6 years at the latest. These “transient early wheezers” do not have a family or personal history of atopy but present an impaired lung function at birth which usually resolves by the age of 7 years (55,56). Respiratory viral infections are the most common causes of wheezing episodes and lower respiratory-tract wheezing illnesses (such as bronchiolitis) during infancy (57). A small percentage of those non-atopic children will continue to wheeze through late childhood. These “non-atopic toddler wheezers” often have a history of several lower respiratory viral infections during the 1st year of life. They are more likely to develop airway obstruction in relation to viral infections later in life, but wheezing episodes usually become less frequent by adolescence (55,57). A third group of children, which accounts for about 20% of all wheezing infants, will have persistent IgE-mediated wheezing leading to chronic asthma. These “atopic wheezers” have a family or personal history of atopy. Their lung function is normal during the first years of life, but typically becomes impaired and associated with bronchial hyper-reactivity by the age of 6 years (55,57).

There is an increasing amount of evidence to support the notion that VD is closely related to host defensive reactions against respiratory tract pathogens (5,58). Over the past twenty years, since the discovery of the greater severity and susceptibility to tuberculosis infection in subjects with low 25(OH)D serum levels (59), the number of publications showing relevant associations between VDD and respiratory infections in children has rapidly increased (5). VD-deficient children have been shown to have a higher risk of both upper and acute lower respiratory tract infections (60-63). These associations have

been further supported by three recent interventional trials, which have demonstrated a reduction of respiratory infection rates in children receiving VD supplements (64-66). VDD has also been seen to correlate with an increased risk of respiratory viral co-infections, especially RSV and rhinovirus infections, which are considered the main triggers of childhood wheezing and have been strongly linked to subsequent development of asthma (67-70). This was documented by Jartti et al., who found that low 25(OH)D serum levels were inversely associated with the risk of both RSV and rhinovirus infections in children hospitalized for acute wheezing (71). A direct link between VDD and RSV-induced bronchiolitis has recently been pointed out by Mansbach et al. (72,73), and has been confirmed in a prospective study by Belderbos et al., who reported that a VD-deficient status at birth was associated with a 6-fold increased risk of RSV-induced bronchiolitis in early life (74). Moreover, in a very recent prospective study on a population-based birth cohort with a 5-year follow-up, cord blood 25(OH)D levels were seen to have an inverse association with the risk of respiratory infections in offspring by 3 months of age, and of wheezing by 15 months, 3 years, and 5 years of age. However, an association between cord blood 25(OH)D levels and doctor-diagnosed asthma by the age of 5 years was not observed (75).

Interestingly, recent prospective studies have suggested that low maternal VD intake during pregnancy may increase the risk of childhood wheezing. In a birth cohort study in the U.S. on 1,194 mother-child pairs, Camargo et al. demonstrated that a 100-IU increase in VD intake during pregnancy decreased the risk of “recurrent wheezing” in offspring at 3 years of age, which is considered a strong predictor of airway remodeling and subsequent asthma development (76,77). In another birth cohort study in Scotland, maternal total VD intake during pregnancy was seen to reduce the risk of both ever and persistent wheezing in children at 5 years of age, with a further association between lower maternal total VD intake and reduced response to bronchodilators in their offspring (78). Finally, a more recent prospective study in Japan reported that infants whose mothers consumed ≥ 172.4 IU \cdot day $^{-1}$ of VD during pregnancy ran a significantly lower risk of wheezing and eczema than children whose mothers had consumed lower doses of VD (79). However, the main limitation of these three studies is that information concerning VD intake during pregnancy was obtained only through food frequency questionnaires, which is not as objective a method as measuring serum 25(OH)D levels. Furthermore, in a very recent population-based birth cohort study in Spain, higher maternal circulating 25(OH)D concentrations during pregnancy were seen to have an inverse association with respiratory infections in offspring in the first year of life, but not with the development of wheezing (at age 1 or 4 years) or asthma at age 4-6 years (80).

6. VITAMIN D DEFICIENCY AND ASTHMA

The prevalence of asthma has increased dramatically since the early 1960s (81). Currently, asthma

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is a public health epidemic, which affects more than 300 million people worldwide, with developed countries furthest away from the equator having the highest prevalence. It is the most common chronic disease of childhood in the world and it is one of the leading causes of morbidity in children which entails a significant social and financial burden (82).

Research efforts have attempted to explain the cause of the rise in the prevalence of the disease, in particular in industrialized countries. In recent years, several studies have focused on the possible causal association between VDD and the burden of asthma. This hypothesis arose from the original observations that these two conditions share several risk factors, such as inner-city residence (20,82), obesity (13,83) and race/darker skin pigmentation (21). Recently, Litonjua et al. extensively reviewed the potential mechanisms of how VD can affect the risk of developing asthma and allergies, including evidence for a role of VD in the immune system and lung development and function, both in utero and in early life (84). In light of these suggested in utero effects, we can speculate that maternal VD status during pregnancy may affect the risk of the offspring developing asthma. Two birth cohort studies have shown that maternal VD intake during pregnancy was inversely associated with the risk of recurrent wheeze, asthma and allergic rhinitis in early childhood, even though these studies were limited by a relatively short duration and the lack of serum VD measurements during pregnancy and infancy (76,85). Furthermore, in a longitudinal birth cohort study in Australia, Hollams et al. found that low VD levels at 6 years of age were significant predictors of subsequent atopy/asthma-development in boys at 14 years of age, although this study lacked serum VD assessment in early life and had an inadequate follow-up (86).

On the other hand, a prospective study of British children reported that maternal serum VD levels > 75 nmol/L (> 30 ng/ml) during late pregnancy was positively associated with a 5-fold increased risk of asthma in offspring at age 9 years, suggesting that even VD supplementation could be a risk factor for asthma and allergic diseases. However, this study was strongly limited by substantial loss (61.8%) to follow-up at 9 years, and results were reported without adjustment for potential confounders (87). In a very recent birth cohort study by Morales et al. (80), maternal circulating 25(OH)D levels during pregnancy were seen to have an inverse association only with the risk of respiratory infections in offspring, but not with wheeze at age 1 or 4 years, or asthma between ages 4 and 6 years. Likewise, in a population-based birth cohort study in New Zealand, Camargo et al. showed that the cord blood 25(OH)D levels of 922 newborns were inversely associated with respiratory infections and wheezing illnesses in early childhood, but not with incident asthma at 5 years of age (75).

Recent studies have also been examining the potential role of VDD in asthma exacerbation and its morbidity. VD deficient children have been shown to have a greater risk of respiratory infections, which are

considered the most common cause of acute asthma exacerbation (46,47). According to the results of a large population survey (the Third National Health and Nutrition Examination Survey, NHANES III), VD deficient asthmatic children are even at higher risk of respiratory-tract infections (88). These findings are consistent with the hypothesis that VDD can weaken pulmonary antimicrobial responses, particularly in asthmatics (24,25). Further support to this hypothesis comes from a recent randomized, double-blinded, interventional study by Majak et al., which was the first to demonstrate that VD supplements (500 IU/day) given to asthmatic children as adjuvant therapy to inhaled glucocorticoids can reduce the risk of acute asthma exacerbation triggered by respiratory infections (89).

VDD has been reported to both increase airway hyper-responsiveness and decrease pulmonary function. In a longitudinal study of 1024 North American children with mild-to-moderate persistent asthma, Brehm et al. found that VD deficiency or insufficiency (defined as a $25(\text{OH})\text{D} \leq 30$ ng/ml) at baseline was associated with a higher likelihood of hospitalization for severe asthma exacerbation during the 4 years of the trial (90). These findings confirm previous results of a cross-sectional study by the same group of researchers on 616 asthmatic children in Costa Rica, in whom serum VD levels were inversely associated with indicators of asthma severity such as airway hyper-responsiveness, hospitalization for asthma and use of inhaled glucocorticoids (91). In addition, two cross-sectional studies on Italian children with asthma found that VD levels were positively correlated with better asthma control and inversely correlated with bronchial reactivity to exercise (92,93).

Finally, it has been suggested that VD enhances the therapeutic response to glucocorticoids in "steroid-resistant asthma". In a cross-sectional study of 100 asthmatic children and adolescents (aged 0-18 years), Searing et al. found that lower VD levels were associated with increased inhaled/oral corticosteroid use and impaired lung function (94). Through an in vitro model of steroid resistance, this study also showed that VD increased responsiveness to glucocorticoids in the peripheral blood mononuclear cells of asthmatics. These findings are consistent with a previous in vitro study and suggest new intriguing perspectives of treatment for patients with steroid-non responsive asthma (95,96).

The precise role of VD in the pathogenesis of asthma is still debated and needs further assessment. Published studies on the topic have had conflicting results and most of them are observational (9). However, in light of increasing evidence of the beneficial effects of VD on asthma and its morbidity, several on-going trials are testing whether VD supplementation can either prevent or improve control of the disease. Currently, two on-going clinical trials are testing whether VD supplementation during pregnancy reduces the incidence of recurrent wheezing and asthma in children by 3 years of age. Results will be available by March 2014 (97) and June 2014 (98), respectively. A third on-going clinical trial is testing whether high dose VD supplementation (2000 IU/day)

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during wintertime in children 1-5 years of age with and without asthma can reduce the incidence of upper respiratory infections and asthma exacerbation. Results will be available by May 2013 (99). Findings from these and future interventional trials need to be evaluated before VD supplementation can be firmly recommended as a preventive or secondary treatment for asthma.

7. CONCLUSION

In conclusion, current evidence strongly suggests a causal association between low VD status during pregnancy and early life and the risk of developing respiratory infections and wheezing in childhood. VD also seems to reduce the risk of acute asthma exacerbation triggered by respiratory infections and to increase the response to glucocorticoids. Although the pathogenetic mechanisms involved are not yet completely understood, emerging data suggests an independent association between VVD and development of asthma. In light of the vast amount of literature on the positive effects of VD on childhood wheezing and asthma, we must consider VD supplementation as a further opportunity to understand and treat these increasingly common conditions. Well-designed randomized, double-blinded, controlled trials on VD supplementation are needed to decipher its role in the prevention and treatment of childhood wheezing and asthma, as well as to define optimal VD levels, optimal timing and duration of such intervention.

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Abbreviations: VD: vitamin D; VDD: vitamin D deficiency; 25(OH)D: 25-hydroxyvitamin D; 1,25(OH₂)D: 1,25-dihydroxyvitamin D; RSV: respiratory syncytial virus

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