REVIEW ARTICLE

Asthma, allergy and respiratory infections: the vitamin D hypothesis

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Abstract

The recent discovery that every tissue in the human body has vitamin D receptors and that vitamin D has pleiotropic effects has prompted an increased interest in this hormone. Vitamin D deficiency is widespread and on the increase. There is no consensus on the serum vitamin D levels to consider appropriate for global health, the cutoffs for its deficiency, or the doses to use for its supplementation. Vitamin D seems to correlate closely with host reactions against various respiratory infections. Epidemiological studies have shown that low serum 25-hydroxyvitamin D levels are associated with a higher risk of upper and lower respiratory infections in children and a shortage of vitamin D may contribute to asthmatic patients' symptoms and morbidity rates. There are studies highlighting associations between childhood asthma, fetal lung and/or immune development, and maternal vitamin D intake. An insufficiency of this vitamin also seems to be implicated in the onset of childhood atopy and food allergies. The hypothesis is that vitamin D could have a central role in these pathological situations and that it may represent a novel preventive and/or therapeutic strategy. This article reviews and discusses published data on the relationship between vitamin D and asthma and allergy, emphasizing the need for controlled, prospective studies on vitamin D supplementation to clarify whether it has a role in the prevention of and treatment for asthma and allergic conditions.

Vitamin D and how it relates to human health are topics that have been attracting much interest of late, and there has been a rapid increase in recent years in the number of publications concerning vitamin D and asthma, allergies, and respiratory infections (Fig. 1). Many effects of vitamin D have been found to occur outside the feedback-controlled osseous endocrine loop and to be independent from serum calcium, phosphorus, or PTH levels. This discovery, together with the realization that essentially every tissue and cell in the body has vitamin D receptors (VDRs) (1), has prompted new interests in the vitamin D system and its previously unrecognized actions. Recent studies point to vitamin D deficiency being associated with many nonskeletal conditions such as cancer, autoimmune diseases, metabolic syndrome, cardiovascular diseases, and respiratory disorders (1). Humans acquire 10% of their vitamin D via ingested foodstuffs (oily fish and cod liver oil) and 90% by synthesis after exposure to sunlight. The epithelia contain high levels of the alpha-1-hydroxylase enzyme that converts the circulating prohormone 25OH vitamin D3 into its active form (1,25 OH vitamin D3), which binds to VDRs (Fig. 2) (2). Recent observational studies in healthy adults and children have documented a widespread vitamin D insufficiency (3–5), especially in non-Hispanic black and Hispanic children, with a seasonal pattern (serum levels are higher in summer). Extrapolating these data, it can be estimated that millions of children worldwide have low vitamin D levels (3), probably due to a combination of behavioral factors (e.g. more time spent indoors, sunscreen use for skin cancer prevention, and clothing coverage) and intrinsic factors (e.g. skin melanin content, a lower production and higher destruction of vitamin D in the skin) (3, 6–8). Obesity has also been associated with low serum levels of vitamin D, probably mainly due to lifestyle issues, as well as to the fact that vitamin D is a fat-soluble vitamin that is taken up by adipose tissues (9–11). As a matter of vitamin D deficiency, physicians should remember that it may also have secondary causes such as covert celiac disease, cystic fibrosis causing malabsorption, and
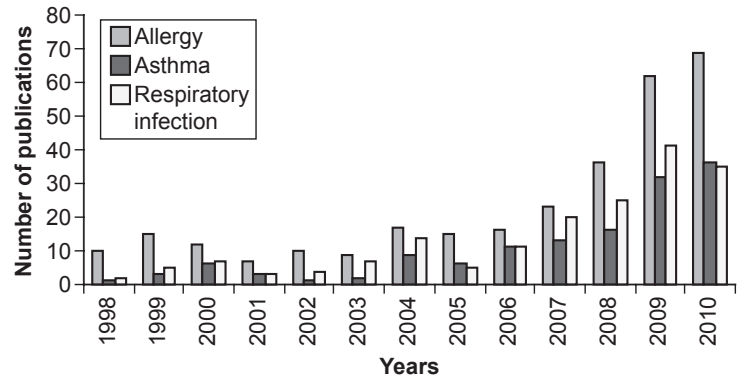
Figure 1 Publications on vitamin D and allergy, asthma and respiratory infections over the past 12 years.
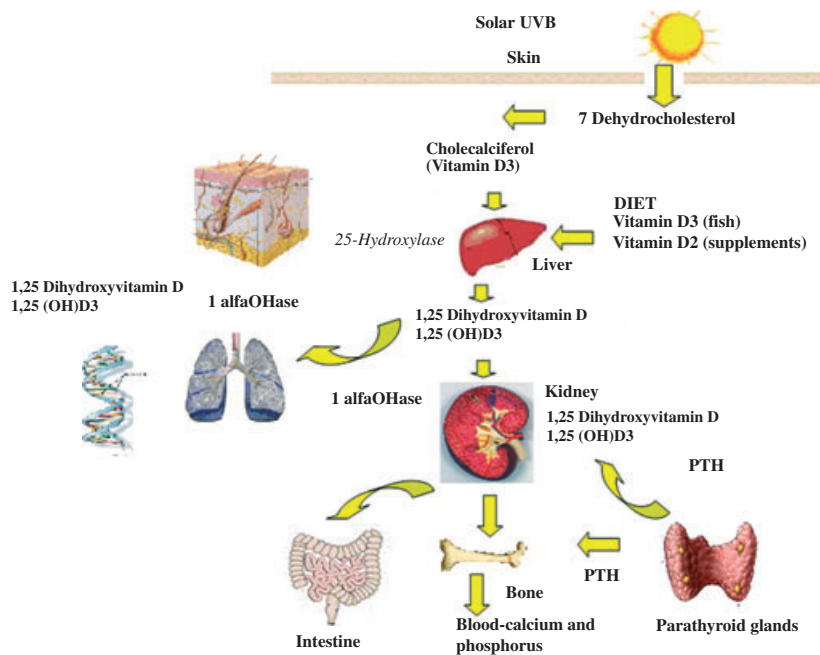
Figure 2 Schematic diagram of vitamin D metabolism. During exposure to sunlight, 7-dehydrocholesterol in the skin absorbs solar UVB radiation and is converted into cholecalciferol (Vit D3). Together with vitamin D originating from the diet, it enters the circulation and is metabolized to 25 hydroxyvitamin D3 (25[OH]D3) in the liver by vitamin D 25-hydroxylase. This is the form that circulates in the highest concentrations and reflects solar and dietary exposure. 25(OH)D3 reenters the circulation and is converted into 1,25(OH)2D3 in the kidney by 25(OH)D3 1 hydroxylase. A variety of factors, including serum phosphorus (Pi) and PTH, regulate the renal production of 1,25(OH)2D, which governs calcium metabolism through interactions with its major target tissues, i.e. bone and intestine. 25(OH)D is also metabolized in other tissues to regulate cell growth (e.g. in the lung and skin) and its expression is controlled by immune signals instead of bone and calcium homeostasis mediators.

medications (e.g. anticonvulsants, rifampicin, and antiretroviral drugs).

Search strategy and selection criteria

In this review, we seek to highlight current knowledge and concepts regarding vitamin D and its actions on respiratory infections, asthma, and allergy in children. We also considered the effects of vitamin D supplementation on pregnant women and newborns. The main databanks considered were Medline and PubMed, and we searched for English-language original studies, reviews, and commentaries. We considered articles published until January 2011 and only studies conducted on children and adolescents aged 0–18 years, except in the case of studies on skin diseases, where we also considered new findings coming from adult literature. The

terms used for the search were vitamin D and all of the following, separately and in combination: deficiency/insufficiency/serum levels/supplementation/immune system/respiratory infection/asthma/wheezing/allergic diseases/food allergy/atopy/maternal intake/vitamin D-binding protein (VDBP)/vitamin D receptor.

Vitamin D serum levels and requirements

Vitamin D status is best assessed by measuring circulating 25-hydroxyvitamin D (25OHD), which is the main circulating vitamin D metabolite with the most potent biological effects. Liquid chromatography–tandem mass spectrometry in isotope dilution is currently considered the gold standard technique for determining an individual's vitamin D status in the blood (12), but several other less specific methods are available, such as radioimmunoassay (RIA), enzyme-linked immunoassay (EIA, ELISA), and chemiluminescence technologies (13). Vitamin D deficiency is defined as a serum concentration < 20 ng/ml (50 nmol/L), and vitamin D insufficiency as a serum concentration between 21 and 29 ng/ml (50–70 nmol/L). These data were determined considering the biomarkers of bone health such as changes in alkaline phosphatase, bone density and calcium absorption, as well as evidence of rickets (14). The Institute of Medicine's Committee (IOM) (15) in the new 2011 report on dietary requirements concludes that dietary reference intake for vitamin D can only be established according to bone health outcomes, not according to other outcomes (e.g. respiratory health), for which the evidence is still insufficient. The report estimated that children over 1 year old need at least 600 IU of vitamin D a day, with a maximum upper limit of 2500 IU for children aged 1–3 years, 3000 IU for children from 4 to 8 years old, and 4000 IU/day for children aged 9 or more years old (15). The current Guidelines from the Section on Breastfeeding and the Committee on Nutrition of the American Academy of Pediatrics recommend a minimum daily intake of 400 IU of vitamin D for all infants, children, and adolescents, starting soon after birth (16). On the other hand, Holick (14, 17) estimated that teenagers and adults need at least 2000 IU of vitamin D a day to meet their body's requirements. Concerning serum levels, the 2011 IOM Committee targeted a serum level of at least 50 nmol/L of 25(OH)D as meeting the needs of nearly all children, in agreement with the Pediatric Endocrine Society (18). Taken together, these considerations show the lack of any general consensus on what serum vitamin D levels are necessary for global health or the doses to recommend for its supplementation (15). It has also been suggested that current cutoffs may underestimate the real needs. A potential obstacle to the clinical use of vitamin D may be its possible (albeit rare) hypercalcemic effect, and that is why drug developers are exploring active vitamin D analogs that minimize the risk of hypercalcemia (19). In addition, data from modern genomewide association studies show that at least three different genes (encoding three key enzymes, 7-DHC reductase, the liver 25-hydroxylase CYP2R1, and CYP24A1) contribute to the variability in serum vitamin D concentrations. These genes may also influ-

ence response to vitamin D supplementation, as recently demonstrated by Schlingmann et al., who described a mutation in CYP24A1 that explained the greater sensitivity to vitamin D of patients with idiopathic infantile hypercalcemia. As the authors suggested, such a mutation could be a genetic risk factor for the onset of symptomatic hypercalcemia triggered by vitamin D prophylaxis in apparently healthy infants. We should also remember these issues when considering vitamin D supplementation (20).

Vitamin D and the immune system

There is plenty of evidence to show that vitamin D is closely related to host reactions against different infections, and the tissue-specific synthesis of the active form of vitamin D (25OHD3) is implicated for both the innate and the adaptive immune systems. It has been demonstrated that vitamin D has potent immunomodulatory properties, exerting an action on cells of the innate immune system to inhibit proinflammatory cytokine production and induce antimicrobial peptide synthesis (21). During a bacterial infection, macrophages acquire the capacity to convert circulating 25 vitamin D into 1,25 OH vitamin D, which is a direct inducer of the expression of genes encoding for antimicrobial peptides and cathelicidin antimicrobial peptide in particular. This peptide is central in host defense against respiratory tract pathogens; it is a vanguard of innate immune response and enhances the clearance of bacteria from various barrier sites and immune cells (22). There is also evidence of vitamin D strengthening the physical epithelial barrier by stimulating junction genes, thereby aiding natural defenses (23). In addition, vitamin D modulates the adaptive immune system via direct effects on T-cell activation and on the phenotype and function of antigen-presenting cells. Vitamin D is associated with a dose-dependent reduction in the transcription of Th-1 cytokines, such as IL-2, granulocyte–macrophage colony-stimulating factor, and interferon gamma, as well as with an increased expression of the Th-2 cytokines IL-4, IL-5, and IL-10 in adult peripheral blood cell cultures. Von Essen et al. (24) recently showed that vitamin D directly modulates the T-cell antigen receptor, which has a central role in T-cell activation. Most of these actions are mediated by VDRs and by the VDBP, a serum protein binding most of the circulating vitamin D. Active VDRs affect the transcription of at least 913 genes (25) and have been recognized as having different genetic variants that can influence the antimicrobial action of vitamin D (via the regulation of T-helper cell development and the cytokine secretion profile) (26), and different VDR variants may be involved in the development of vitamin-D-related diseases (27). Vitamin D-binding protein seems to have immunomodulatory functions relevant to lung biology, and variations within its gene seem to be associated with infectious airway diseases involving a different level and efficacy of macrophage activation and neutrophil chemotaxis (28). In conclusion, it has been established that vitamin D is a modulator of innate and adaptive immune system functions and has a key role in Th1–Th2 balance.

Vitamin D and respiratory infections

It has long been thought that by inducing muscle weakness (especially of the diaphragm and intercostal muscles), vitamin D deficiency gives rise to difficulties in eliminating respiratory secretions and thus facilitates the development of infections. A decreased serum 25OH vitamin D concentration and increased severity and/or susceptibility to tuberculosis infection have been demonstrated by several studies published over the past twenty years and recently reviewed (29). These concepts now need to be integrated with new discoveries on the role of vitamin D in the respiratory system. The well-known association between infections and vitamin D deficiency was first described more than a century ago. Children with rickets and even those with subclinical vitamin D deficiency were more likely to develop pneumonia, and this was observed in children in India (30), Ethiopia (31), Kuwait, Yemen, and Turkey (32–34). Wayse et al. (30) found that exclusive breastfeeding and adequate serum 25OHD3 were significantly associated with a lower risk of severe acute lower respiratory tract infections (ALRTI) in Indian children without rickets. Likewise, the study by Karatekin et al. (34) on vitamin-D-deficient, but not rachitic, Turkish newborns showed that the risk of ALRTI increased significantly with serum vitamin D concentrations lower than 10 ng/ml. Leow et al. (35) recently reported that vitamin D deficiency is associated with a higher mortality among patients with community-acquired pneumonia, and McNally et al. (36) showed that significantly more children admitted to pediatric intensive care units with ALRTI were more deficient in vitamin D than other children with less severe ALRTI or controls without infections. Vitamin D deficiency has also been seen to increase the risk of upper respiratory tract infections (URTI) and viral coinfections (37). A direct link has been found between the seasonality of influenza and respiratory syncytial virus (RSV)-induced bronchiolitis and vitamin D deficiency (which is also more common in winter) (38, 39). A prospective birth cohort study demonstrated that children who are vitamin D deficient at birth have an increased risk of developing RSV respiratory infections in the first year of life (40). A large cross-sectional study on the US population reported that vitamin D status is inversely associated with recent URTI, and interventional trials demonstrated fewer respiratory tract infections in children receiving vitamin D supplementation (41, 42). The link between vitamin D deficiency and respiratory infections becomes particularly relevant in children with respiratory diseases such as asthma (37, 43). In a study on National Health and Nutrition Examination Survey data, lower vitamin D levels were associated with a higher adjusted odds ratio for recent URTI, especially among patients with asthma (43). In a small randomized, double-blinded, interventional study, Majak et al. (44) were recently the first to demonstrate that vitamin D supplementation (500 IU/day) in children with asthma from September to July reduced the risk of asthma exacerbation triggered by respiratory tract infections. In short, these studies support a role of vitamin D in defense against upper and lower respiratory infections but further randomized, controlled trials on the effect of vitamin D supplementation on clinically relevant infection outcomes will be needed to confirm any immunological role of vitamin D supplementation.

Vitamin D and asthma

The relationship between asthma and vitamin D has been the subject of several studies in the past 10 years. Although most of these studies support a protective effect of vitamin D, there are also some reports suggesting that a vitamin D supplementation can instead be a risk factor for asthma and other atopic disorders (45). In a birth cohort study in Finland, for example, subjects regularly given vitamin D supplementation in the first year of life (about 200 IU/day) had a marginally significant higher risk of asthma, atopy, and allergic rhinitis at 31 years of age than unsupplemented controls (46). In addition, a Swedish study demonstrated that vitamin D intake >400 IU a day in 5-month-old infants correlated significantly with the risk of eczema at 6 years of age (47).

On the other hand, several epidemiological studies have suggested that vitamin D deficiency is associated with an increased incidence of asthma and allergy symptoms (46, 48–53), and a number of hypotheses have been advanced to explain the pathogenetic link between asthma and vitamin D deficiency. As mentioned earlier, vitamin D deficiency may weaken pulmonary defenses against respiratory infections and this would contribute to the triggering of asthma exacerbations caused by respiratory tract infections. This was suggested by Jartti et al., (37) who found that serum 25OH vitamin D levels were inversely associated with RSV and rhinovirus infection in wheezing children necessitating hospitalization. There is an increasing body of evidence to support the hypothesis that infections carry a greater morbidity in asthmatic subjects than in the healthy population, indicating a weaker antiviral response in asthmatics (53). In a study on children in Costa Rica (52), lower vitamin D levels were associated with increased airway responsiveness and higher eosinophil counts and IgE levels, while higher vitamin D levels were associated with a lower likelihood of hospitalization for asthma exacerbations. These findings were confirmed by the same group of researchers in a subsequent study based on the CAMP cohort of 1024 children, apart from the association between vitamin D levels and allergy markers (IgE levels and eosinophil counts) (54). The authors suggest that higher vitamin D levels may help to control infections and reduce inflammatory responses, resulting in viral infections causing less severe symptoms and sequelae. A second aspect involved in the relationship between vitamin D deficiency and asthma relates to lung function impairment. Children with insufficient vitamin D levels were found to have a slightly lower mean FEV1 than children with sufficient vitamin levels (54); similar lung function results were obtained in adolescents and adults too (55–57). In a recent pediatric study conducted by Chinellato et al. (58) a significant correlation was found between predicted FVC% and serum 25(OH)vitamin D, and the children with well-controlled asthma had higher serum levels of vitamin D. In a further study, the same group showed an association between vitamin D and an increased

bronchial reactivity to exercise (59). Zosky et al. (60) recently demonstrated in an animal model that vitamin D deficiency causes lung function impairments primarily involving differences in lung volume, providing direct mechanistic evidence of a link between vitamin D and lung development, which may explain the association between obstructive lung disease and vitamin D status. A third aspect of the relationship between vitamin D and asthma relates to the possible role of vitamin D in airway remodeling. Vitamin D has been shown to influence the microarray gene expression signature in bronchial smooth muscle cells (61), with consequent effects on remodeling, cell growth and survival, morphogenesis and the extracellular matrix. This suggests a role of vitamin D in airway remodeling, which may be important in asthma pathophysiology and treatment (62). The functions of vitamin D also depend on individual VDR and VDBP variability. Together with different levels of vitamin D, VDR and VDBP variants seem to represent a risk factor for asthma (63).

Vitamin D may also affect the efficacy of anti-asthma therapy. The most effective anti-inflammatory treatments available are glucocorticoids. A study by Searing et al. (64) demonstrated a significant association between lower vitamin D levels and a greater use of inhaled and oral corticosteroids. One explanation for this finding might be that lower vitamin D levels contribute to a more severe asthmatic condition; another possibility is that vitamin D affects the glucocorticoid pathways and vitamin D deficiency makes it necessary to administer higher doses to achieve a therapeutic effect. The hypothesis that vitamin D supplementation might potentiate the anti-inflammatory function of corticosteroids is intriguing because glucocorticoid resistance or insensitivity is an important barrier to effective treatment in some patients with asthma (64). There is also some evidence of vitamin D supplementation in glucocorticoid-resistant patients with asthma being able to enhance their subsequent response to dexamethasone by inducing the production of IL-10 (a potent anti-inflammatory cytokine) from regulatory T cells. This was demonstrated *in vitro* by Xystrakis et al., and also in a recent study by Searing et al., in which vitamin D also enhanced the action of glucocorticoids in peripheral blood mononuclear cells from patients with asthma (64–66).

An important aspect to be considered when evaluating the relationship between asthma and vitamin D deficiency is the effect of possible confounders, such as race or socioeconomic status. In fact, although vitamin D insufficiency is widespread, the lowest levels are reported in non-Hispanic black children and in Hispanic children that are also the populations with the highest prevalence of asthma (3). Nonetheless, it has been shown that even after correcting for race, there is a significant association between asthma and vitamin D deficiency (54). Moreover, Freishtat et al. (50) in a study evaluating only African-American children, confirmed that asthmatic subjects have lower vitamin D levels compared with healthy controls.

To sum up, although the pathogenetic mechanisms involved have not been completely understood and although the role of potential confounders should always be consid-

ered, the available data strongly suggest an independent association between vitamin D deficiency and asthma (3, 50, 54).

Vitamin D and allergic diseases

Considering the pleiotropic effects of vitamin D (especially on the development of immune system tolerance and of the integrity of the epithelial barrier), recent studies have hypothesized a relationship between the hormone vitamin D and the rising incidence of food allergies and skin diseases. According to epidemiological studies, the incidence of food allergy is increasing among children and its pathogenesis remains unclear. In 2007, Camargo et al. (51) observed a strong north–south gradient for the prescription of epinephrine autoinjectors (EpiPens) in the United States, hypothesizing a link between low vitamin D levels in the north and allergic disorders; other epidemiological north–south trends have been observed for vitamin D deficiency and food allergy (based on A&E department records and hospitalizations), which probably correlate with a different UVB exposure (51, 66–69), although there is no direct evidence of such a causal link. A recent study by the National Health and Nutrition Examination Survey 2005–2006 found vitamin D deficiency (< 15 ng/ml) associated with higher levels of IgE sensitization to food and environmental allergens in children and adolescents (70). Intestinal infections, abnormal barrier permeability, and the promotion of a prosensitization immune balance as a result of vitamin D deficiency may contribute to the onset of food allergy. Vitamin D also seems to be involved in the development of many skin diseases (psoriasis, eczema, etc.), and VDRs have been found in basal proliferating keratin cells (71). We know from experience that most atopic patients have fewer skin lesions in summer, and we cannot rule out a potential effect of exposure to sunlight and the consequent increase in vitamin D production. In a study conducted in children with atopic dermatitis, Peroni et al. (72) found a clear association between vitamin D deficiency and severity of atopic dermatitis. Hata et al. (73) published a study on vitamin D supplementation in patients with atopic dermatitis, measuring cathelicidin expression in normal and atopic skin biopsies before and after vitamin D supplementation (4000 IU a day for 21 days). They found that oral vitamin D supplementation can correct the cathelicidin deficiency in the innate immune system of atopic subjects. Thorp et al. (74) demonstrated that adult patients with chronic urticaria have lower vitamin D levels than controls, supporting the conviction that vitamin D may be an important immunomodulator.

Maternal vitamin D and the risk of wheezing and atopy in offspring

It has been demonstrated that fetal life, with its genetic and epigenetic phenomena, is crucial as regards any future development of chronic diseases, including asthma and allergies, and there has been growing interest in the influence of early-life and prenatal dietary exposure on the development of asthma and allergic diseases. There are studies highlighting

associations between childhood asthma, fetal airway and/or immune development, and maternal intake of some nutrients (vitamin E, Se, and polyunsaturated fatty acids) during pregnancy. Vitamin D has been implicated in lung development (75–77) and maturation, and it has been suggested that there is an alveolar vitamin D paracrine system (78). For the time being, no international guidelines are available on vitamin D supplementation during pregnancy. In a recent study by Camargo et al. (79) on a population-based birth cohort with an excellent 5-year follow-up, cord-blood 25-hydroxyvitamin D levels were seen to have a significant inverse association with the risk of respiratory infections and childhood wheezing, but no association with incident asthma. Epidemiological data point to a possible inverse association between a mother's vitamin D intake during pregnancy and her child wheezing (80–82) or developing rhinitis at 5 years old (83). This correlation was found in different populations, regardless of the different amounts of vitamin D intake. In a study by Devereux et al. (82), the inverse association between maternal vitamin D intake during pregnancy and the risk of childhood wheezing was independent of maternal smoking status or vitamin E, zinc, and calcium intake, or of the child's vitamin D intake. On the other hand, a prospective study in the United Kingdom reported that children whose mothers had higher serum concentrations of 25OH vitamin D in late pregnancy (>75 nmol/L) carried a significantly greater risk of visible eczema on examination at 9 months old and of asthma at 9 years old (84). A problem with many of these studies is that the data concerning vitamin D intake were based only on food frequency questionnaires (80, 82) or reports of supplementation (48). Although such methods have been validated and are representative of intake over a period of time, they are not as objective as serum level measurements. Future interventional studies with longitudinal cohorts are needed to establish whether changes in maternal nutrient intake during pregnancy can be used as a healthy low-cost public health measure to reduce the prevalence of childhood asthma and atopy. A randomized trial supported by the US NIH has already started on vitamin D supplementation in pregnant women (4000 IU/day) and the onset of asthma in their children; the results will be available by June 2014 (85). Such studies will be very important in shedding light on the vitamin D hypothesis in fetal life.

Conclusions

In recent years, numerous studies have been published on the effects of vitamin D, which seems to have a role in many different diseases (autoimmune, cardiovascular, allergic disorders, etc.). Rickets is no longer considered a common disease, but vitamin D deficiency seems to be widespread and may occur without many of the signs of nutritional rickets. A limit of the present review is that the studies considered sometimes differ somewhat in defining deficient and insufficient vitamin D levels, because there is no general consensus on such definitions. The variations are small but they may nonetheless constitute an important bias. It would be important to arrive at definitions of the optimum serum level and the levels coinciding with vitamin D deficiency or insufficiency, not only for osseous outcomes but also for global health. A crucial issue for any vitamin D intervention concerns its dosage. The currently recommended vitamin D levels are thought to be the bare minimum needed for its beneficial effects on muscle and skeletal function, but the optimal vitamin D levels for global health (immune system function, possible prevention of atopy and defense against respiratory infections) are still not known. In light of recent literature on the action of vitamin D, and the effects it has demonstrated *in vivo* and *in vitro* in asthma and atopic disorders, it seems that this hormone might lead to a new turning point in our understanding and treatment of these increasingly common conditions. Well-designed clinical trials on vitamin D supplementation are needed to provide a definitive answer to the hypothesis that vitamin D could have a role in the prevention of and treatment for asthma, allergic diseases, and respiratory infections in childhood.

Conflict of interest

None.

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