Vitamin D and asthma

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ABSTRACT

The mechanisms for the aetiology and pathobiology of allergy and asthma are currently matters of hot debate in the scientific world. Each week it seems that a new theory for their origins is proposed, new evidence for causation is discovered and new suggestions for prevention are extrapolated. It is highly likely that allergy occurs in the human host when tolerance to environmental allergens fails to occur. This process is most obvious in early infancy. The link between allergy and asthma is another leap of faith. It is most likely that the mechanisms that develop to predispose a human subject to asthma are only partly linked to allergy. Other factors and processes must be occurring at least synergistically to produce the asthma phenotype. Finally, even when asthma occurs its phenotypic expression has a myriad of syndromes. One of the topical phenomena in the overlay of all of these conditions is vitamin D deficiency and insufficiency. Again probably, given the evidence, vitamin D is linked to allergy and asthma disease states. However, before we rush to attribute these common problems to a nutritional defect we need significantly more information that vitamin D replacement will aid in therapy or prevention. The risk of not doing so is that the 'cure' for asthma is ascribed to a 'natural product' and our patients are led gullibly off in the wrong direction.

THE AETIOLOGY OF ALLERGY

It is becoming increasingly clear that allergy occurs when allergen tolerance fails to take place.[1] Although this process may occur at any age, it typically occurs in early infancy. The process of tolerance is facilitated largely in the neonatal and infant gut, and is referred to as oral tolerance. Three factors are instrumental in the success of oral tolerance: normal microbial gut flora colonisation; antigen encounter; and a host of non-specific immunomodulatory factors (Fig. 1). It appears that all
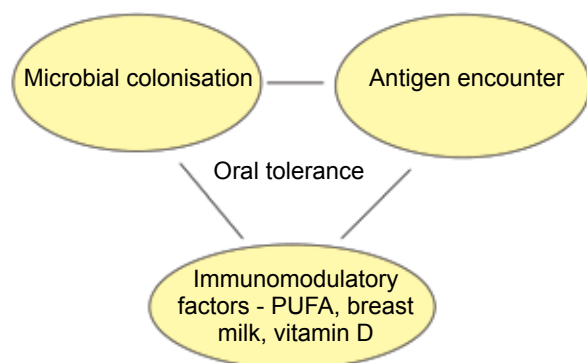

Fig. 1. Factors operational in allergic aetiology (PUFA – polyunsaturated fatty acid).

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of these factors operating together promote oral and systemic allergen tolerance. Development of allergy can thus be thought of as a process resulting from lack of development of antigen tolerance; this process operates on a genetically predetermined basis.

THE AETIOLOGY OF ASTHMA REVISITED

The aetiology of asthma is a subject of much debate and research. The prevailing paradigm that asthma is linked to atopy is under review. It seems that less than 40% of all asthmatics are atopic and other phenomena are sought to explain asthma onset. These factors are listed in Table I.

Table I. Possible aetiological factors for asthma[1]

Atopy

Bacterial super antigens

Pollutants (indoor, tobacco smoke, vehicle emissions)

Dietary factors (allergens, lack of immunomodulatory factors (including vitamin D deficiency), genetically modified foods, toxins, dietary salt and magnesium)

Lack of physical activity

Obesity

Drugs (including paracetamol)

In an asthmatic individual the process of inflammation results in airway hyperresponsiveness followed by variable airway obstruction and finally symptoms (cough, wheeze, tight chest and shortness of breath) (Fig. 2).[2]

Inflammation forms an integral part of the pathogenesis of asthma (Fig. 3). There seems to be an imbalance in the CD4 T helper 1 (Th1) and T helper 2 (Th2) responses. Th1 response is primarily involved in cell-mediated immunity, where Th2 responses form part of the antibody-mediated immune response. Asthmatic airways are characterised by increased Th2 activity, with increased IgE secretion mediated by interleukin-4 (IL-4) and IL-5, resulting in airway hyperresponsiveness. IL-4 and IL-13 switch B-cell production to IgE synthesis, and IL-5 helps with eosinophil maturation. IL-13 regulates airway hyperresponsiveness and mucus gland hyperplasia. Interferon-gamma (IFN-γ) is responsible for suppressing the production of IgE.[3]

Factors thought to be responsible for the rising prevalence of asthma

As the genetic pool of asthma cannot change rapidly over time, it seems logical that environmental factors are responsible for differences in asthma prevalences. Since Wesley et al.[4] suggested that traditional rural lifestyles protected against asthma and that urbanisation thus promoted asthma development, many authors have speculated about mechanisms for the phenomenon.

Atmospheric pollution, dietary changes, changes in allergen load, improvements in health and hygiene (the hygiene hypothesis) and lifestyle changes have all been proposed for this phenomenon.[5] The Durban Harbour Basin Study[6] would suggest a strong case for atmo-
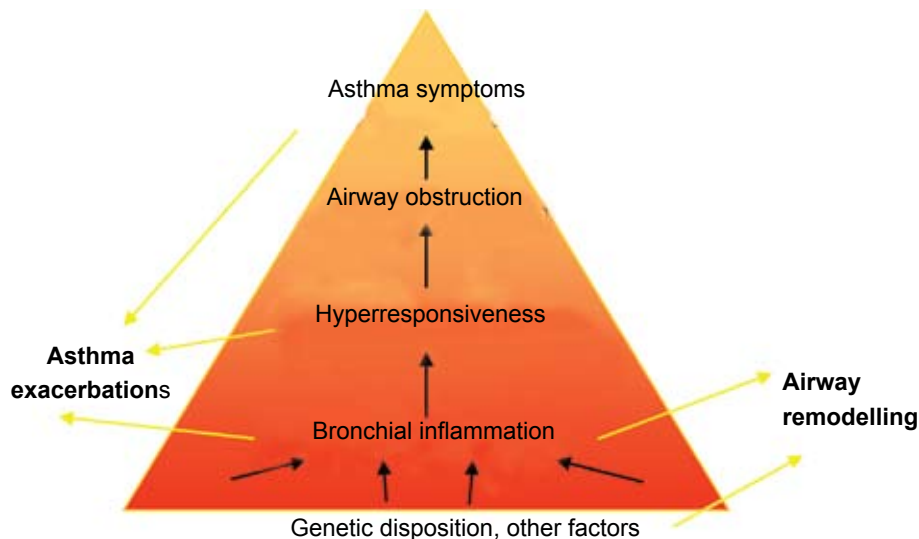
Fig. 2. The relationship between asthma pathophysiologies.

Asthma symptoms

Airway obstruction

Hyperresponsiveness

Bronchial inflammation

Genetic disposition, other factors

Asthma exacerbations

Airway remodelling

modification of gene expression via epigenetic mechanisms are also likely to be important. Antenatal exposures that increase the risk of asthma include tobacco smoke, and ambient and indoor air pollution. Impacts of maternal nutrition and maternal diseases, such as asthma and diabetes, are also important. Early-life environmental exposures may also increase the risk of asthma via impacts on lung growth and immune maturation. Synergistic interactions between viral lower respiratory infections and allergic sensitisation in early life appear to be especially important in increasing the risk of subsequent asthma.

spheric pollution while the findings of the Gauteng School Study[7] supports the hygiene hypothesis. In this study it was found that children who lived in 'shacks' (i.e. poorer socio-economic conditions) were less likely to have asthma than their well-off peers. Studies in the Cape have suggested that changes in allergen load and atopic status mirror the rising prevalence of this condition. It seems clear that no one factor is responsible for asthma aetiology and that the condition is probably multifactorial in aetiology as well as clinical expression.

There is increasing evidence that several potentially overlapping genetic predispositions may contribute to the development of asthma. These include: predisposition to abnormal lung growth, resulting in lower lung function; delayed immune maturation; predisposition to lower respiratory viral infections; early allergic sensitisation; and predisposition to bronchial hyperresponsiveness. Networks of genes and environmental

ACUTE ASTHMA EXACERBATIONS

An acute attack of asthma can be defined as an acute exacerbation of wheeze or coughing, unresponsive to usually effective therapy and necessitating care in an emergency room or hospital ward. An acute attack is characterised by airways narrowing and inflammation, hyperinflation, impairment of pulmonary function, alteration in alveolar ventilation and hypoxaemia.

Acute attacks result from failure of long-term therapy (non-adherence) or exposure to triggering agents, e.g. viruses causing colds or 'flu, grass, tree, or weed pollens, animal dander from cats or dogs, moulds, or house-dust mites. The commonest causes of acute
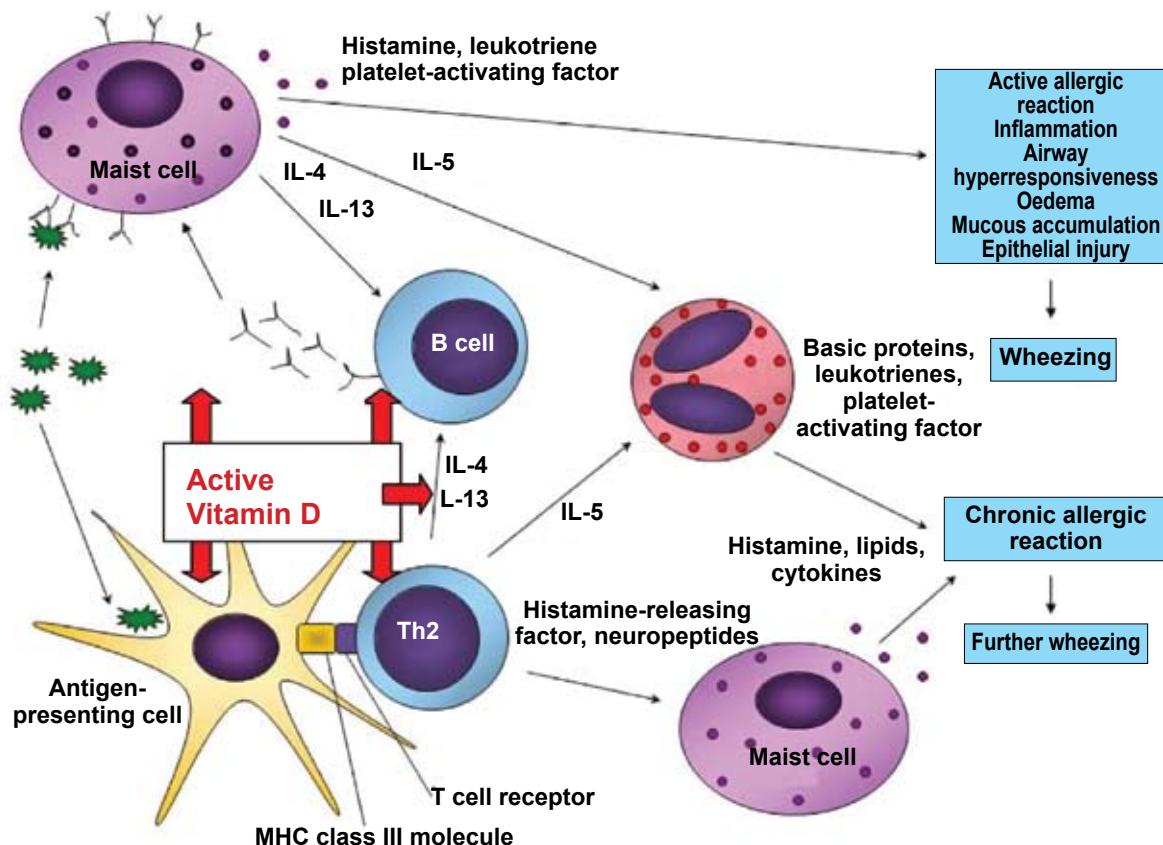

Fig. 3. The pathophysiology of an atopic asthmatic response and sites of Vitamin D impact.

asthma are viral upper respiratory tract infections. Bacterial infections are not regarded as triggers of asthma and consequently routine antibiotic therapy is not indicated.

The human rhinovirus (HRV) is the commonest trigger for acute asthma. Up to 80% of asthma exacerbations are triggered by a 'cold'. The HRV is a picornavirus, a small RNA virus of which 100 serotypes have been described. A major group (accounting for 90% of all serotypes) uses ICAM-1 as a cellular receptor. Of the 3 serotype groups (A,B,C), C is responsible for more virulence and replicates in both the nose and lower respiratory tract (LRT) and produces more severe and prolonged infection in asthmatics.[8]

However, recently, additional culprits for both aetiology of chronic and acute asthma have been sought.

VITAMIN D – ROLE IN LUNG IMMUNOMODULATION

Vitamin D is produced by the conversion of provitamin D to previtamin D in the skin during exposure to sunlight. Ultraviolet radiation in the band 290-315 nm causes this effect. Some vitamin D comes from food sources. Previtamin D is converted in the liver to 25-hydroxyvitamin D. The active form of vitamin D is 1,25-dihydroxyvitamin D (1,25(OH)2D3) which is generated primarily in the kidneys (Fig. 4).[9] 1,25(OH)2D3 binds to cell membrane vitamin D receptors and forms a complex that is then internalised. Vitamin D receptors form part of the steroid hormone nuclear receptor complex. This complex binds to the vitamin D promoter region of the vitamin D responsive genes that influence the rate of RNA polymerase II-mediated transcription. It has been found that different gene polymorphisms of the vitamin D receptor have variable associations with asthma.[10]

The serum 25-hydroxyvitamin D level is the best indicator of overall vitamin D status. Skin-derived vitamin D is variable and depends on pigmentation, latitude, season, clothing, age, sunscreen use and local weather patterns.[9] Frank vitamin D deficiency (serum levels of 25-hydroxyvitamin D below 25 nmol/l) causes rickets and a characteristic clinical syndrome. However vitamin D insufficiency (levels between 25 and 75 nmol/l) has become a topic of much debate. This syndrome is not associated with a clear clinical definition. The condition may be associated with cardiovascular disease, diabetes mellitus, cancer and immune dysfunction.

Understanding of vitamin D metabolism and biological effects has grown in recent times, and it is emerging that vitamin D has many immunomodulatory effects. Despite its systemic role, 1,25(OH)2D3 also seems to have a paracrine role as has been described in monocytes, T cells, B cells and dendritic cells (Fig. 3). This is supported by the fact that all these cells have the ability to metabolise vitamin D via CYP27B1 expression and their ability to activate vitamin D via 1α-hydroxylase expression.[11]

The enzyme, 1α-hydroxylase, is present and expressed in airway epithelium (in significant quantities) and a host of lung constitutive and inflammatory cells including alveolar macrophages, dendritic cells, and lymphocytes.[12] These cells are important in inducing the expression of cathelicidin and cytokines like CD14. These cytokines and bacteriocidal peptides modulate the inflammatory response in the airways.[13] Vitamin D3 has various specific effects on different immune cells.

Vitamin-D-deficient patients have decreased chemotactic and phagocytic activity of macrophages. This can be reversed by supplementation with vitamin D.[14] Antimicrobial activity of macrophages against *Mycobacterium tuberculosis* is increased in the presence of cholecalciferol. This has been known for decades as increased sun exposure helped in treatment of patients with tuberculosis.[15] This is mediated by the up-regulation of cathelicidin via the hCAP-18 gene and induction of the defensin 2 gene. Furthermore 1,25(OH)2D3 inhibits the expression of inflammatory cytokines in monocytes, including IL-1, IL-6, tumour necrosis factor-alpha (TNF-α), IL-8, and IL-12.[14]

1,25(OH)2D3 promotes apoptosis and inhibits maturation of bone-marrow-derived mast-cell precursors. There was also a dose-dependent inhibition of mast-cell differentiation by 1,25(OH)2D3 at various stages of mast-cell development.[16]

Vitamin D plays a role in B-cell functioning by the inhibition of plasma-cell differentiation and immunoglobulin secretion (IgG and IgM), memory B-cell generation and apoptosis of activated B cells. Cholecalciferol inhibits the differentiation of B lymphocytes to plasma cells and memory B cells. These mechanisms may contribute to the pathogenesis of B-lymphocyte-related diseases like asthma.[17]

Vitamin D inhibits proliferation of Th lymphocytes. The effect of cholecalciferol on Th-mediated cytokines is variable, enhancing and suppressing secretion under
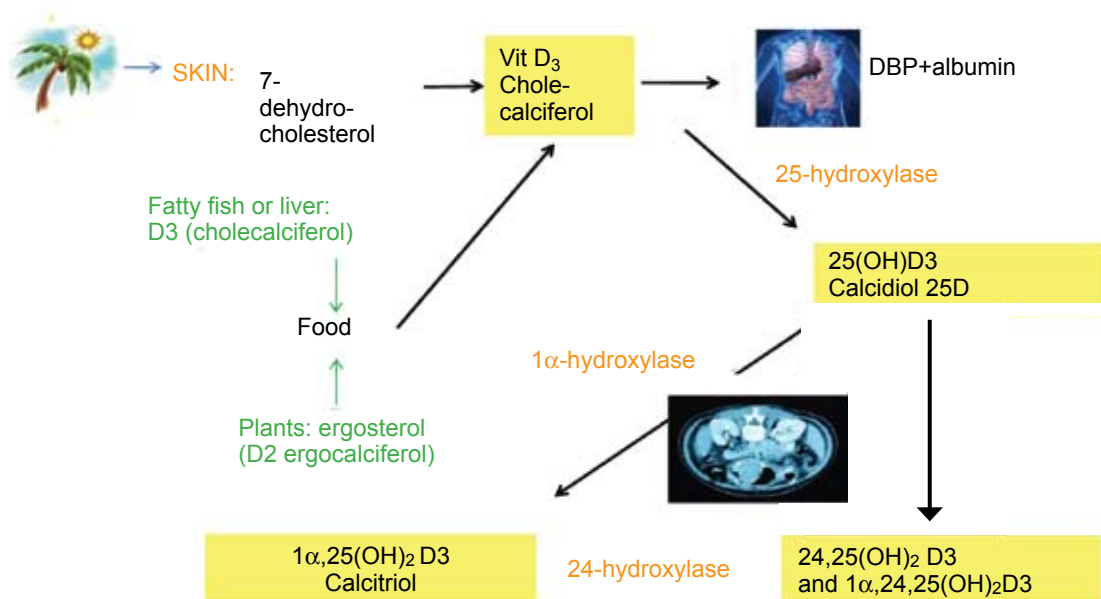

Fig. 4. Vitamin D metabolism (DBP – vitamin D binding protein).

different circumstances. Vitamin D receptors seem to increase with maturation of T cells, being least present in naive T cells.[18] 1,25(OH)2D3 inhibits the synthesis of the Th1 cytokines, IFN-γ and IL-2, as well as the Th17-derived cytokines IL-17 and IL-21.[19] It also suppresses Th2 differentiation through IL-4 and IL-13 suppression.[20] The overall effect though, seems to be a shift in the expression of cytokines from a Th1 response towards a Th2 type response.[21,22] The main effect of vitamin D on cell-mediated immunity occurs indirectly through alteration of antigen-presenting cells, especially dendritic cells. Th17 cells produce the cytokine IL-17. This cytokine is involved in neutrophil-driven responses. The production of IL-17 has been reported to be inhibited by vitamin D. Vitamin D is an important regulator of lymphocyte trafficking and homing, to sites of inflammation.[23,24]

The response of dendritic cells to vitamin D is restricted to myeloid dendritic cells, these express a different set of toll-like receptors and cytokines to plasmacytoid dendritic cells.[25] Vitamin D inhibits the maturation and differentiation of these dendritic cells characterised by the down-regulation of expression of the costimulatory molecules CD40 and CD80/CD86.[26] Vitamin D further inhibits the production of IL-12 and IL-23 (the major cytokines driving Th1- and Th17-differentiation respectively). 1,25(OH)2D3-modulated dendritic cells have a reduced capacity to trigger T-cell proliferation.[27] This in conjunction with the enhanced IL-10 production, results in decreased T-cell activation, inducing immunological tolerance. These tolerogenic dendritic cells are also capable of inducing CD4+CD25+ suppressor T cells.[28]

The vitamin D receptor was found to be present in bronchial smooth-muscle cells which are associated with active protein synthesis. 1,25(OH)2D3 arrests the progression of airway smooth-muscle cells in the S phase of the cell cycle. This happens without affecting cell apoptosis. It has been demonstrated that 1,25(OH)2D3, inhibits platelet-derived growth factor that induces bronchial smooth-muscle DNA synthesis.[29] The metalloproteinases (MMPs) 9 and 33 (ADAM33) are believed to play a role in airway remodelling.[30] Another important aspect of airway remodelling is angiogenesis. It is believed that 1,25(OH)2D3 blunts the growth response to angiogenic stimuli such as thrombin and platelet-derived growth factor.[31]

All these effects operating at a cellular level could be advantageous to protection against infection and the development of allergic lung diseases like asthma.[32,33]

VITAMIN D DEFICIENCY, ALLERGY AND ASTHMA AETIOLOGY AND ACUTE ASTHMA ASSOCIATION

Vitamin D deficiency is increasing worldwide. Vitamin D deficiency causes the paediatric disease rickets. In addition, there is some evidence that vitamin D deficiency and insufficiency may lead to other diseases including those associated with immune-dysregulation including asthma.

A potentially large number of individuals may have vitamin D insufficiency especially during winter months. Seasonal decrease in vitamin D concentrations can be correlated with the increased numbers of LRT infections.[34] The Third National Health and Nutrition Examination Survey (NHANES III) has shown an association between serum vitamin D levels and respiratory infections.[35]

One author has suggested that 'the four key nutritional risk factors for acute lower respiratory tract infection disease burden globally are macronutrient undernutrition, low birth weight, zinc deficiency and suboptimal breastfeeding'.[36] Also of importance are nutritional status and vitamin D deficiency in determining infection risk.

Both animal models and studies in human fetal tissues show that vitamin D plays a role in fetal lung growth and maturation. Epidemiological studies have also suggested that higher prenatal vitamin D intakes have a protective role against wheezing illnesses and asthma in young children.[37,38] One study has suggested that higher vitamin D intake by pregnant mothers reduces asthma risk by as much as 40% in children 3-5 years old and evidence is available to suggest that vitamin D deficiency is associated with increased airway hyper-responsiveness, lower pulmonary functions, worse asthma control, and possibly steroid resistance.[39] Other studies show a strong relationship between serum concentrations of cholecalciferol, forced expiratory volume in 1 second (FEV$_1$), and forced vital capacity, where decreasing pulmonary function is associated with vitamin D deficiency.[39,40]

Glucocorticoids form the mainstay of treatment of the inflammatory component of asthma. Patients with chronic asthma who are unresponsive to high doses of glucocorticoids and are without confounding factors have been termed glucocorticoid-resistant.[41] Glucocorticoids inhibit both cell-mediated and humoral immune responses. Glucocorticoids induce the synthesis of IL-10, a potent anti-inflammatory and immunosuppressive cytokine. Glucocorticoids reduce the humoral response by inhibition of cytokine production by Th2 cells, as well as reducing mast cell and eosinophil function and modulation of IgG4:IgE ratios. The production of IL-10 plays a central role in disease activity control in asthma.[42]

Glucocorticoid-resistant asthma is defined by an FEV$_1$ less than 75% of predicted, with failure to improve by 15% after an adequate dose and duration of glucocorticoid therapy (e.g. 40 mg/day of prednisolone for 1-2 weeks). Steroid resistance has been linked to chronic airway remodelling.[41] Failure to induce IL-10 synthesis forms a major component of glucocorticoid resistance.[43] A potential source of IL-10 includes the Tregs, a CD4 subset of T-regulatory cells. The Tregs are responsible for regulating and co-ordinating the Th1/Th2 and Th17 activity. With the addition of vitamin D$_3$ the defect in glucocorticoid-induced IL-10 secretion in steroid-resistant patients is overcome. Vitamin D$_3$ has also been shown to overcome ligand-induced down-regulation of glucocorticoid receptors.[44]

CONCLUSION

It must be obvious that no one factor should be held accountable for the aetiology of allergic diseases, asthma or acute asthma exacerbations. Operating on a genetic basis many factors must play a role. What is becoming clear is that the list of such factors is increasing. It seems prudent to be careful of being too didactic in ascribing aetiology to asthma and allergy. Even the vitamin D evidence is still tenuous and while some individuals with asthma may well have vitamin D insufficiency or even deficiency and may well benefit from supplementation, this therapy should not be seen as a panacea. We think this is especially important considering the potential for the 'cure' of asthma to be ascribed to a dietary supplement or 'natural remedy'.

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