REVIEW ARTICLE

Biological Roles of Vitamin D and Immunoglobulin E: Implications in Allergic Disorders

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ABSTRACT

Many factors contribute to the development, progression and management of allergies. Immunoglobulin E (IgE) has a well-established role in allergic disorders and vitamin D has also been implicated in some forms of allergy. Vitamin D is a fat-soluble secosteroid hormone which is actively responsible for calcium balance and bone health. It also plays important roles in regulating neuromuscular function, cellular differentiation, insulin secretion and blood pressure. IgE, produced by the B-lymphocytes, is primarily involved in mediating hypersensitivity. It is associated with anaphylaxis and other forms of allergic reactions. It also plays several other vital roles in the immune system such as functional activation of T cells and wound healing. Low serum vitamin D is associated with the onset of asthma and atopic dermatitis by triggering IgE-mediated type-1 hypersensitivity but at the same time supra-normal serum vitamin D levels are also associated with the IgE hypersensitivity in allergic conditions including psoriasis, dermatitis and rhinitis. No clear association has been established between serum IgE and vitamin D levels in IgE-mediated allergies but has been suggested to maintain normal serum vitamin D levels for potential protection against the development of IgE-mediated allergic disorders. The current review summarizes the biological roles of vitamin D and IgE, particularly in the context of allergic disorders. The currently available evidence points to altered serum vitamin D levels and disturbed vitamin D signaling as a possible reason for IgE mediated allergies but more data needs to be gathered through future studies to ascertain definitive clinical impact.
Keywords: Vitamin D, Immunoglobulin E, Allergy, Hypersensitivity

INTRODUCTION

Allergic disorders affect more than one-third of the world's population across all age groups and geographical locations. Allergic disorders can be triggered by various agents including respiratory allergens, food allergens, skin allergens and drugs. Many factors have been implicated in the development, progression and management of allergies. These include genetic predisposition, environmental influences, nutritional status and various biochemical factors. Immunoglobulin E (IgE) is one such factor which has a well-established role in allergic disorders. Vitamin D has also been shown to play potentially beneficial roles in some types of allergic disorders. The present work summarizes the biological functions of vitamin D and IgE and reviews the evidence gathered so far about the role of vitamin D and IgE in allergic conditions.

Vitamin D is a fat-soluble vitamin and secosteroid hormone naturally produced in the skin following exposure to sun light[1] which converts the 7-Dehydrocholestrol to cholecalciferol (vitamin D_3)[2]. Vitamin D_3 is then converted to 25-hydroxyvitamin D in liver by cytochrome P-450 based enzyme 25-hydroxylases[5] and later in kidney 1-alpha hydroxylases produces 1,25-dihydroxyvitamin D (calcitriol) by hydroxylation of calcidiol[14]. Vitamin D being synthesized by skin is not sufficient in many cases therefore supplementation is required[5]. It is actively responsible for calcium balance and bone health and also plays important roles in regulating neuromuscular function, cellular differentiation, insulin secretion and blood pressure[6]. Besides these, vitamin D also serves several other vital functions including immunomodulatory as well as antioxidant effects[7]. Vitamin binds to the vitamin D receptor (VDR) which are located in nucleus that modulate transcription, thus regulating cellular functioning[8,9]. Vitamin D receptor (VDR) acts on vitamin D response elements (VDRE) which eventually take charge of transcriptional control of genes[10].

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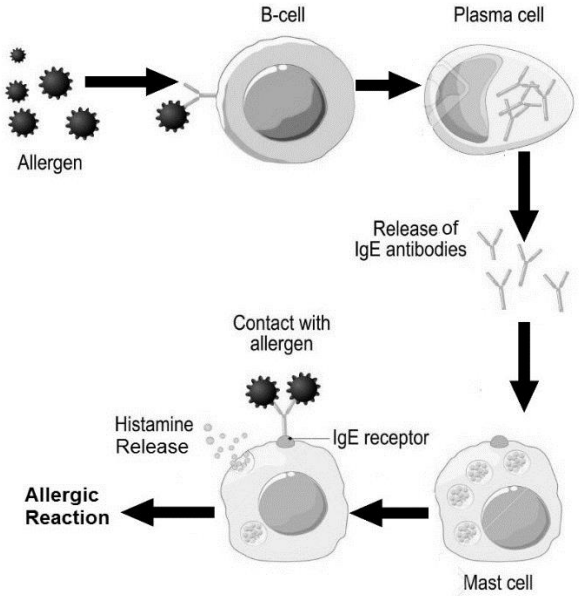
Vitamin D deficiency is a common health problem the world over with prevalence in Middle Eastern populations reaching up to 80%[11]. Vitamin D deficiency is also associated with insulin resistance, poor peripheral glucose uptake and impaired glucose metabolism[12] and with onset of several cancers as ovarian cancer[8]. With growing awareness of the importance of vitamin D in human health, the risk of vitamin D toxicity has also been increasing due to excessive and unsupervised vitamin D supplementation[13]. Hypervitaminosis D results in the saturation of VDR, which in turn increases the transport of vitamin D binding protein (VDBP) into cells provoking transcription via activation of nuclear receptors[14]. These undesired transcriptional events result in toxic manifestations including gastrointestinal problems like vomiting, diarrhea and abdominal pain[15]. cardiovascular complications such as hypotension, arrhythmias and degree heart block[16], renal dysfunction, neuropsychiatric symptoms, pancreatitis and hypercalciuria[17].

Immunoglobulin E (IgE) are produced by the B-lymphocytes following cytokine stimulation by interleukin-4 (IL-4) and interleukin-13 (IL-13)[18]. IgE is normally present in a very minute amount in the body but its synthesis is triggered by foreign particles that act as allergens. Increased IgE production triggered by allergens results in hypersensitivity response characterized by allergy and anaphylaxis[19]. The normal serum concentration of IgE ranges between 150-300 UI/ml (or below 110 ng/dL)[20,21]. IgE is primarily thought to be involved in hypersensitivity reactions but it plays several other vital roles in the immune system such as functional activation of Th2 cells and wound healing[18]. In fact, the hypotension resulting from anaphylactic shock is actually a protective mechanism that hinders circulation and gives the immune system time to resolve and/or eliminate the toxin from body[19,22].

In allergic conditions, IgE acts aa reactive immunoglobulin that crosslinks to a particular antigen and deters its further hazardous effects[23]. Hyper IgE syndrome (HIES) is indicative of infections primarily cutaneous staphylococcal and fungal infections[24]. It is manifested in the rashes, abscesses, pulmonary infections and mucocutaneous candidiasis[25]. In

sensitized /previously exposed allergic patients, B cells upregulate IgE production which eventually results in class switching of immunoglobulins i.e., from normal IgG to IgE on exposure to any foreign particle in mucosa and mucosal secretions making them prone to more allergic attacks[26]. IgE hypersensitivity is also involved in parasitic infections[27]. as well as IgE mediates basophils to release cytokines and chemokines to combat again parasitic actions[28].

Figure 1: Mechanism of IgE-mediated allergic reactions



Mechanism of immunoglobulin e-mediated allergy: Allergens mediate the release of immunoglobulins, thereby triggering hypersensitivity reactions which are mostly IgE mediated type 1 reactions (Figure 1)[1]. IgE usually manifests its allergic actions via two receptors FcεRI and CD23 (FcεR2)[29]. In allergic states, Fc receptor plays a key role as its antagonist omalizumab is the only biological treatment for asthma at present[30]. IgE is associated with anaphylaxis and allergic reactions[31] and almost one-third of the world's population is affected from hypersensitivities of various types[32]. On exposure to allergens/ microbes / toxins, B- cells produce specialized plasma cells as well as memory cells and on re-exposure to toxin/allergen and with aid of memory cells, germinal center derived IgG producing plasma cells switch to IgE production that leads to IgE hypersensitivity[33].

There are several types of IgE-mediated allergies such as respiratory allergies, food allergies, skin allergies and drug allergies. Each type of allergy is caused by a specific trigger and has its characteristic clinical presentation e.g. food allergy may be caused by a specific food item and leads to inability to metabolize that food item along with other allergic symptoms. A Finnish study reported that infants who suffered from rickets developed food allergies more commonly, possibly due to deficiency of vitamin D, but the exact mechanism is unknown[22]. Allergies can be of infective or microbial origin. Allergies are also commonly caused by environmental agents such as pollen, dust, smoke, fog and smog. These environmental allergies typically manifest either in the form of respiratory problems like bronchial asthma or in the form of anaphylaxis[1,7,34,25]. Drug allergies can vary ranging from cutaneous manifestations as hives, skin rashes and pruritus to hypotension leading to cardiovascular collapse[36,37]. Different types of IgE mediated allergies are assessed using various clinical and serological parameters but a raised serum IgE titer is considered the gold standard especially in rhinitis, rhinosinusitis, skin allergies and in drug allergies (Table 1)[38]. Besides serum IgE, eosinophilia and positive skin prick test or nasal allergen challenge are good indicators of allergy[39]. Studies have also reported markedly reduced vitamin D levels in many allergic conditions, indicating an inverse relation with serum IgE levels[40,41].

Vitamin d and immunoglobulin-e mediated allergy: Vitamin D has been a topic of debate in the last two decades after the identification of its multiple biological roles in human health and disease. Mechanistic and clinical evidence that has emerged over time has strongly established IgE as a key allergic mediator. A growing body of scientific evidence has since implicated vitamin D in IgE-mediated allergic processes and diseases. Most studies have pointed to a protective role of vitamin D against allergies, but a few studies have yielded contradictory results.

Vitamin D deficiency has been suggested as a key element in development and progression of allergic conditions. Vitamin D deficiency is closely associated with the type 1 hypersensitivity, especially in the allergic progression of asthma. Adequate vitamin D status and VDR signaling have been shown to be potentially protective against asthma by helping lung maturation and growth, preventing infections and regulating immune system (Figure 2). The down regulation of VDR signaling due to vitamin D deficiency induces the production and proliferation of B-lymphocytes sensitized by interleukin-13 (IL-13). The resultant enhanced production of IgE leads to onset, progression and/or exacerbation of allergy[42]. Vitamin D has also been associated with protection and prevention of asthma, allergic disorders and recurrent respiratory disorders due to the induction of cathelicidin antimicrobial peptide-37 (LL-37), which has anti-viral, anti-fungal and anti-bacterial actions[35]. LL-37, produced in cells especially in macrophages, natural killer cells (NK-cells), and epithelial cells of the skin, airways, and intestine following induction by vitamin D, also controls cell death and autoimmunity and regulates multiple signaling cascades and inflammatory pathways[43]. Another important but lesser known function of vitamin D is tissue growth and remodeling via collagen synthesis and inhibition of metalloproteinase enzymes[16].

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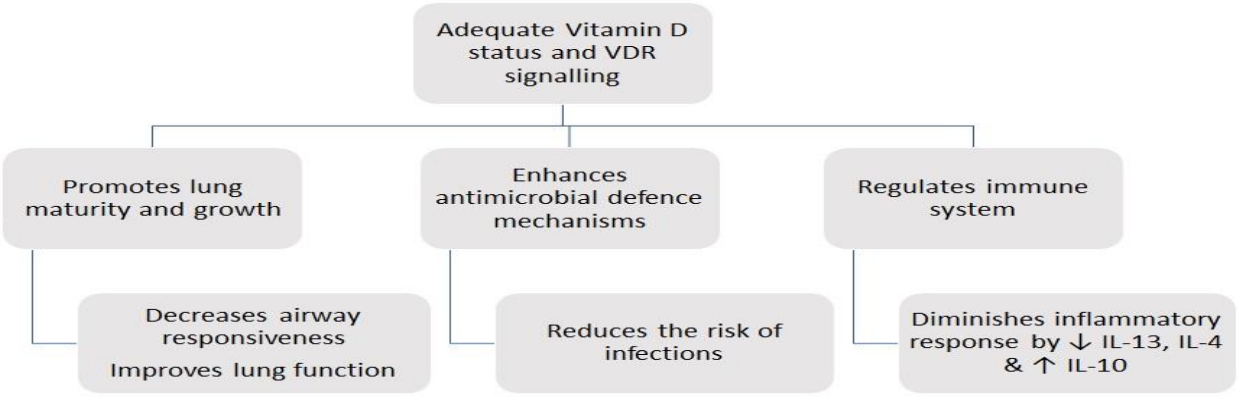
Table 1: Biomarkers of IgE-mediated allergy

Allergic conditions	Vitamin D levels	IgE levels	Other biomarkers
Asthma	Decreased level is a triggering factor	++++	Monoclonal antibodies
Rhinitis	Subnormal due to remodeling of bronchial mucosa	+++	Skin prick test (SPT), Nasal Allergen Challenge, Osteopontin.
Rhinosinusitis	Decreased levels a triggering factor	++++	Eosinophilic infiltration, Charcot-laden crystal proteins
Skin Allergies	Normal/ subnormal	+++	Mononuclear infiltrates, Eosinophilia
Drug Allergies	Reduced level a triggering factor due to low transcription of proteins	+++	Neutrophilia, Eosinophilia and hypotension

Figure 2. Potential protective mechanisms of vitamin D and VDR signaling against the development, progression and exacerbation of allergic asthma



Vitamin D is actively responsible for the remodeling of airways by inhibition of smooth muscle hyperplasia, with potentially beneficial effects in asthma[42]. Activated vitamin D (1α-25-dihydroxyvitamin D3) hinders the activation, maturation and functioning of the dendritic cells (DCs), resulting in the suppression of antigen presentation[7]. It is also associated with the anti-inflammatory effects of T-regulatory cells and balances the ratio of T-helper-1 (Th1) and T-helper 2 (Th2) cells[35]. Due to these key roles played by vitamin D, its deficiency has been shown to predispose to a variety of allergic disorders including asthma and eczema[42,44]. Vitamin D deficiency has been shown to cause airway hyper-responsiveness, thereby lowering pulmonary function, worsening asthma control and increasing steroid resistance[1,6,42]

In a study by Manousaki et al., low serum levels of vitamin D were shown to be associated with the onset of asthma and atopic dermatitis by triggering IgE-mediated type-1 hypersensitivity[45]. Another study on murine models found vitamin D deficiency to be associated with exacerbation of allergic signs and symptoms along with increased pulmonary inflammation and excessive production of cytokines. When the vitamin D deficient mice were treated with vitamin D supplementation, they showed improvement in allergic condition through upregulation of T-helper cells and stabilization of eosinophils and mast cells[34]. A cross-sectional study in Indonesian children having atopic dermatitis observed a negative correlation between serum vitamin D levels and a clinical index of severity of atopic dermatitis[46]. Naghizadeh et al. assessed correlation of serum vitamin D and IgE with various allergic parameters in Iranian students with allergies. While a positive correlation between serum IgE and allergies was observed, no correlation was shown between vitamin D and IgE[41]. A study by Muehleisen et al. yielded the interesting finding that both subnormal and supra-normal serum vitamin D levels are associated with the IgE hypersensitivity in allergic conditions including psoriasis, dermatitis and rhinitis[47]. The role of IgE in development of parasitic infections has also been debated for quite some time. Results from a study by Malpica et al. suggested that in patients with Strongyloides stercoralis infection, IgE production was markedly enhanced due to increase in T-regulatory cell response as compared compared to healthy controls[48]. Contrarily in an experimental mice model study by Ridi et al., IgE failed to influence the outcome of infections by Schistosoma mansoni both exogenously as well as endogenously.[49] Interestingly, a study by Martinez et al. suggested a protective role of vitamin D in Leishmaniasis[50].

CONCLUSIONS

Based on the studies conducted so far, no clear association can be established between serum IgE and vitamin D levels in IgE-mediated allergies. Preliminary biochemical and clinical evidence points to altered serum vitamin D levels and subsequent disturbances in the vitamin D signaling pathway as one of the possible reasons for onset and progression of IgE mediated allergies but larger, comprehensive studies are required to elaborate this further and furnish definitive clinically useful insights. Based on the available data, it is advisable to maintain normal serum vitamin D levels for potential protection against the development of IgE-mediated allergic disorders.

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