Vitamin D Deficiency and Its Relation to Allergic Diseases: A Cross Sectional Study Among Allergic Patients from Jeddah City, Saudi Arabia

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Abstract

Objective: In this cross-sectional study, we aimed to estimate the prevalence and trend of sensitization to common aeroallergens and food allergens among allergic patients and investigate the relationship between their atopic profile and vitamin D level.

Methods: A total of 918 patients referred to King Fahd General Hospital Immunology Laboratory in Jeddah city; Kingdom of Saudi Arabia (KSA), with clinical manifestations or suspicion of respiratory and/or food allergies were included in the study. They underwent tests for total and allergen-specific serum IgE (sIgE). Vitamin D data was available for 222 sensitized patients.

Results: Out of 918 patients, 383 cases exhibited positive sIgE to either one or more allergens (41.7%). Indoor allergens were the most common type of aeroallergens followed by grass pollens, molds and tree pollens. The most frequent indoor allergen panel was House Dust Mites (HDM) and cockroach panel. It included Dermatophagoides pteronyssinus and Dermatophagoides farina with (31.2 %) and (30.9%) prevalence respectively, then cockroach German (14.2%), followed by cat dander (9.3%) and dog dander (9.2%). The most prevalent grass pollen allergen was Bermuda grass (7.7%), while the commonest mold allergen was
Candida albicans (7.1 %). The top food allergens were shrimp (16%), cod fish (8.3%) and peanut (6%) followed by milk (5.7%) and soybean (5.2%). The majority of the patients had vitamin D deficiency (74.7%) and (12.6 %) had vitamin D insufficiency. Patients with vitamin D deficiency are more liable to have allergic sensitization to different allergens, both food and aeroallergens among all grades than those with insufficient or sufficient levels, especially in high reactivity group (grade 6) in which 95% of patients had vitamin D deficiency.

Conclusion: Sensitization to HDM, cockroach German and cat dander showed an increased prevalence amongst studied patients. The most frequent food allergens were shrimp and codfish. Vitamin D deficiency is significantly noticeable among allergic patients.

Keywords
Atopy; Aeroallergens; Allergic Sensitization; Food Allergens; Vitamin D

Abbreviations
sIgE: Allergen-specific Serum IgE; HDM: House Dust Mite; 25(OH) D: 25-hydroxyvitamin D; DC: Dendritic Cells; FA: Food Allergy; IL: Interleukin; TNF-α: Tumor Necrosis Factor-alpha; IFN-γ: Interferon-gamma; TGF-β: Transforming Growth Factor Beta; CTLA-4: cytotoxic T lymphocyte antigen 4; PD-1: Programmed Death-1.

Introduction
The rising trend in the prevalence of allergic diseases such as respiratory and food allergies were perceptible especially in Westernized community over last few decades, then it has shown further extension to other regions of the world [1]. Accompanying this trend, a parallel increase in allergen sensitization, which proposes that these increases are related [2]. It turned out that contact with aeroallergens such as HDM, tree and grass pollens, or pet dander is tightly associated with sensitization, a key driver in the initiation, continuation and severity of allergic respiratory diseases [3]. The component of the food allergens may trigger allergic immune responses. In fact, relatively few foods (fish, shellfish, peanut, tree nuts, egg, milk, wheat and soy) constitute most of the inflammatory allergic reaction. Those major food allergens share common characteristics, since they are water soluble and fairly stable to heat, acid and proteases. Besides, it has been indicated that the presence of immune-stimulatory factors in food may lead to such sensitization [4].
It has long been known that the predisposition to allergic diseases development is tightly related to genetic background and immunological factors, however many epidemiological studies attributed the variations in the incidence of atopic diseases to the exposure to different environmental stimuli including indoor and outdoor allergens, which have a great impact in disease pathogenesis [5]. Therefore, controlling allergic disease symptoms necessitates identifying the allergens, preventing their contact and ameliorating a specific IgE associated response by allergen immunotherapy. To date, various methods are still used for allergen detection, however practically measurement of sIgE antibody is the wildly ordered in vitro test and it is used to diagnose and monitor patients with allergic conditions [6].

Previous series of experiments demonstrated the immunologic mechanisms used by vitamin D to attenuate the immune response [7]. As a matter of fact, it has been noted that vitamin D insufficiency has taken a part in boosting the incidence of allergic diseases [8]. It has also inspired much interest for its potentially benefit effect in inflammatory disorders through modifying the function of cells classically associated with adaptive immunity, such as decreasing immune receptor expression on monocyte derived dendritic cells (DCs), inhibiting DC activation by lipopolysaccharides and reducing the function of these cells [9,10]. Vitamin D also decreased proinflammatory cytokine release from peripheral blood mononuclear cells in general and from T-cells in particular [11,12]. The aforementioned biological mechanisms support the role of vitamin D in the pathogenesis and treatment of allergic diseases [13].

The objective of our research is to identify the patterns of sensitization to most prevalent respiratory and food allergens amongst allergic patients based on the results of allergen specific IgE and to elucidate the relationship between the serum level of 25-hydroxyvitamin D (as a major circulating form of vitamin D) and their atopic profile.

Subjects and Methods

Subjects

Before commencing, this study granted ethical approval from local institutional review board. It is a cross sectional study in which the study group was selected from all pediatric and adult outpatients and inpatients referred to King Fahd General Hospital Immunology Laboratory with clinical manifestations or suspicion of respiratory and/or food allergies and tested for total and allergen-specific serum IgE in the period of January 2018 up to December 2019 with range of age starting from 1 year and up to 80 years old. A total of 918 consecutive patients were enrolled in the study, among them vitamin D data was available for 222 sensitized patients. The whole data were then analyzed in detail as delineated below.


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Measurement of Total IgE and sIgE

10 ml venous blood samples were withdrawn from each patient then they were tested for total and sIgE using the ImmunoCAP 100 System (Phadia, Sweden). The test based on sandwich immunoassay technique. Inhalant or food allergens or their components or mixture of relevant allergens are covalently bound to a solid phase and allowed to react with the specific IgE in patient serum. This was followed by a washing step to remove away non-specific IgE. After adding enzyme-labelled antibodies against IgE, a complex is formed. Afterward unbound enzyme-labelled anti-IgE is washed away allowing only the bound complex to be incubated with the developing agent. Subsequently stopping solution was added and finally, the fluorescence of elute is measured to assess both inhalant and food allergens for specific IgE. The fluorescence is directly proportional to the concentration of IgE in the serum sample.

The tested inhalant allergens were divided into 7 panels or mixes which contain 35 allergens as follow: house dust mites and cockroach panel (Hollister-Stier Labs, Dermatophagoides pteronyssinus, Dermatophagoides farinae, Cockroach German), animal dander panel (Cat, Dog, Horse and Cow dander), tree pollens panel 1 (Grey alder, Hazel, Elm, Willow, Cotton wood) tree pollens panel 2 (Box-elder, Common silver birch, American beech, Oak, Walnut), weed pollens panel (Goosefoot-Lamb’s quarters, Mugwort, Western ragweed, Plantain-Ribwort and Lenscale), grass pollens panel (Timothy grass, Bermuda grass, Meadow grass, Rye-grass, Johnson grass and Bahia grass) and molds panel (Penicillium chrysogenum, Cladosporium herbarum, Aspergillus fumigatus, Candida albicans, Alternaria alternata and Setomelanomma rostrata). From those mixes which showed positive results, individual allergen testing were done for the following 17 aeroallergens (Dermatophagoides pteronyssinus, Dermatophagoides farina, Cockroach German, Cat dander, Dog dander, Horse dander, Cow dander, Grey alder, Hazel, Common silver birch, Mugwort, Plantain-Ribwort, Bermuda grass, Rye-grass, Timothy grass, Aspergillus fumigatus and Candida albicans).

The food panels included 10 applied allergens which divided into 2 main panels: Sea food panel (Shrimp, Blue mussel, Fish (cod), Tuna and Salmon and another panel which include (Egg white, Milk, Wheat, Peanut, Soybean,). Again from those two panels, cases which reacted positively went to individual allergen testing for the next 7 individual allergens (Shrimp, Fish, Tuna, Egg white, Milk, Peanut and Soybean). Depending on ImmunoCAP 100 System results, sIgE was categorized into 6 grades: Grade 1 (0.35-0.70 KUA/L), grade 2 (0.70-3.50 KUA/L), grade 3 (3.5-17.5 KUA/L), grade 4 (17.5-50 KUA/L), grade 5 (50-100 KUA/L) and grade 6 (more than 100 KUA/L). Level less than 0.35 KUA/L was considered to be negative.

Measurement of Serum 25-hydroxyvitamin D

The level of 25-hydroxyvitamin D (25(OH) D) is used as an indicator of vitamin D status. Quantitative determination of the 25(OH) D in serum samples was performed to 222 positive
sIgE cases using a commercially available chemiluminescence Immunoassay ADVIA Centaur® vitamin D kit (ADVIA Centaur®/XPT, Siemens, Germany). Based on many reviews, vitamin D level more than 30 ng/ml considered to be sufficient, meanwhile a level ranging from 20 - 30 ng/ml classified as insufficiency and between 10 - 20 ng/ml as deficiency, whereas less than 10 ng/ml indicate severe deficiency [14-17].

Statistical Analyses

Data was analyzed using Prism 5 software (GraphPad, La Jolla, CA). Continuous variables were presented as mean and standard deviation while categorical variables as frequency distribution with percentages. Student t-test was used to compare continuous variables meanwhile analysis of variance was utilized to acquire the significant levels of vitamin D based on different categories. P value of less than 0.05 was considered to be significant.

Results

Patient Characteristics

Out of 918 patients, 383 cases exhibited positive sIgE to either one or more allergens (41.7%). Those reacted patients were classified into eight groups according to age (Table 1). Among the reacted patients, females accounted for 57.2% (n=219). Most of the patients (40%) were from dermatology department, followed by pulmonary (21 %) and pediatric departments (20%). Clinical manifestations mainly involved atopic dermatitis, urticaria, allergic asthma, allergic rhinitis, allergic gastroenteritis and chronic sinusitis.

<table>
<thead>
<tr>
<th>Age Groups, Years</th>
<th>Female Number</th>
<th>Male Number</th>
<th>Total Number with Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5</td>
<td>6</td>
<td>14</td>
<td>20 (5.2%)</td>
</tr>
<tr>
<td>6-10</td>
<td>10</td>
<td>10</td>
<td>20 (5.2%)</td>
</tr>
<tr>
<td>11-20</td>
<td>35</td>
<td>32</td>
<td>67 (17.5%)</td>
</tr>
<tr>
<td>21-30</td>
<td>40</td>
<td>20</td>
<td>60 (15.7%)</td>
</tr>
<tr>
<td>31-40</td>
<td>51</td>
<td>42</td>
<td>93 (24.2%)</td>
</tr>
<tr>
<td>41-50</td>
<td>37</td>
<td>19</td>
<td>56 (14.6%)</td>
</tr>
<tr>
<td>51-60</td>
<td>25</td>
<td>18</td>
<td>43 (11.2%)</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>15</td>
<td>9</td>
<td>24 (6.2%)</td>
</tr>
</tbody>
</table>

Table 1: Gender and age groups for all sensitized patients.
Total IgE and Positive sIgE

From those 383 reacted cases, 237 cases (61.9%) exhibited increased total IgE, 134 (35%) were monosensitized while 249 cases (65%) were polysensitized. On the other hand, comparing the level of total IgE among different age groups showed significant difference with the highest level recorded between 6-10 and 11-20 years old (p 0.001) (Fig.1), meanwhile no significant difference between male and female patients (p value = 0.21). Table 2 and Fig. 2 show the number and frequency of patients according to positive sIgE to either aeroallergens or food allergens. Indoor allergens were the most common type of aeroallergens followed by grass pollens, molds and tree pollens. *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* had got the highest frequencies with (31.2%) and (30.9%) prevalence rate respectively. They were followed by cockroach German (4.2%), cat dander (9.3%) and dog dander (9.2%). The main grass pollen allergen was Bermuda grass with sensitization rate of (7.7%) followed by Rye-grass (6.6 %) and Timothy grass (6.1%), while the most frequent mold allergen was *Candida albicans* (7.1%) followed by *Aspergillus fumigatus* (4.5%). On the other hand, Grey alder was the commonest among tree pollens (4.5%). In our study the most notable food allergen was shrimp with (16%) prevalence, followed by fish (8.3%) and peanut (6%). Milk allergy was found at a rate of (5.7%) while soybean was (5.2 %). The least reactive were egg white and tuna with (3.7%) and (2.7%) reactivity respectively.

Figure 1: Comparison of total IgE of 383 sensitized patients among different age groups.

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Table 2: Numbers and frequencies of Aeroallergen and food allergen sensitization and their severity grades among sensitized patients (* HDM: House Dust Mite).

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Numbers</th>
<th>Frequency</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>Grade 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timothy grass</td>
<td>56</td>
<td>6.10%</td>
<td>20</td>
<td>25</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grey alder</td>
<td>41</td>
<td>4.50%</td>
<td>21</td>
<td>13</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hazel</td>
<td>34</td>
<td>3.70%</td>
<td>13</td>
<td>17</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Common silver birch</td>
<td>18</td>
<td>1.90%</td>
<td>4</td>
<td>11</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Shrimp</td>
<td>147</td>
<td>16%</td>
<td>22</td>
<td>91</td>
<td>28</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Tuna</td>
<td>25</td>
<td>2.70%</td>
<td>12</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Egg</td>
<td>34</td>
<td>3.70%</td>
<td>17</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Milk</td>
<td>53</td>
<td>5.70%</td>
<td>16</td>
<td>28</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fish (cod)</td>
<td>77</td>
<td>8.30%</td>
<td>19</td>
<td>37</td>
<td>7</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peanut</td>
<td>55</td>
<td>6%</td>
<td>16</td>
<td>26</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Soybean</td>
<td>48</td>
<td>5.20%</td>
<td>17</td>
<td>22</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Serum 25-hydroxyvitamin D

The current study shows remarkable higher frequency of allergic patients with vitamin D deficiency (74.7%) compared with both vitamin D insufficiency (12.6%) and sufficient vitamin D level (12.6 %) among 222 sensitized patients with p-value 0.001 (Table 3 and Fig. 3). Regarding sIgE the frequency of allergic patients in each grade and the significance of these frequencies in relation to vitamin D level was examined. It was obviously noticed that higher frequencies are always found among patients with vitamin D deficiency compared with both vitamin D insufficiency and sufficient level across the 6 grades with p-value 0.001 (Fig. 4).

Figure 3: Comparison between sensitized patients’ frequencies with different vitamin D levels among 222 sensitized patients (** indicates P < 0.001).
Figure 4: Comparison between sensitized patients’ frequencies within the different grades of sIgE and different scopes of vitamin D in 222 sensitized patients (** indicates P < 0.001; and *** indicates p < 0.0001).

<table>
<thead>
<tr>
<th>Patients’ groups</th>
<th>Number of patients and their percent in each group</th>
<th>&lt; 10 ng/ml</th>
<th>10-20 ng/ml</th>
<th>20-30 ng/ml</th>
<th>&gt; 30ng/ml</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D levels in a group of 222 sensitized individuals</td>
<td>94 72 28 28</td>
<td>94</td>
<td>72</td>
<td>28</td>
<td>28</td>
<td>222</td>
</tr>
<tr>
<td>Percentage (%) among sensitized individuals</td>
<td>42.30% 32.40% 12.60% 12.60%</td>
<td>42.30%</td>
<td>32.40%</td>
<td>12.60%</td>
<td>12.60%</td>
<td></td>
</tr>
<tr>
<td>Positive sIgE test Grade 1 group</td>
<td>66 46 11 9</td>
<td>66</td>
<td>46</td>
<td>11</td>
<td>9</td>
<td>132</td>
</tr>
<tr>
<td>Percentage (%) among Grade 1 group</td>
<td>50% 34.80% 8.30% 6.80%</td>
<td>50%</td>
<td>34.80%</td>
<td>8.30%</td>
<td>6.80%</td>
<td></td>
</tr>
<tr>
<td>Positive sIgE test Grade 2 group</td>
<td>105 76 27 23</td>
<td>105</td>
<td>76</td>
<td>27</td>
<td>23</td>
<td>231</td>
</tr>
<tr>
<td>Percentage (%) among Grade 2 group</td>
<td>45.50% 33% 11.70% 9.90%</td>
<td>45.50%</td>
<td>33%</td>
<td>11.70%</td>
<td>9.90%</td>
<td></td>
</tr>
<tr>
<td>Positive sIgE test Grade 3 group</td>
<td>81 39 12 6</td>
<td>81</td>
<td>39</td>
<td>12</td>
<td>6</td>
<td>138</td>
</tr>
</tbody>
</table>

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Table 3: Prevalence of hypovitaminosis D among sensitized patients.

| Percentage (%) among Grade 3 group | 58.70% | 28.30% | 8.70% | 4.30% |
| Positive sIgE test Grade 4 group | 48     | 24     | 4     | 2     | 78   |
| Percentage (%) among Grade 4 group | 61.50% | 30.80% | 5.10% | 2.60% |
| Positive sIgE test Grade 5 group | 15     | 5      | 5     | 5     | 30   |
| Percentage (%) among Grade 5 group | 50%    | 16.60% | 16.60% | 16.60% |
| Positive sIgE test Grade 6 group | 29     | 5      | 0     | 2     | 36   |
| Percentage (%) among Grade 6 group | 80.50% | 13.90% | 0%    | 5.56% |

Discussion

There is an increasing body of evidence supporting that allergic disease prevalence is increasing in recent years, which has been expected by the WHO and documented in many recent studies worldwide [18-22]. The most effective method in the prevention and treatment of allergic diseases is the assessment of allergen sensitization which allows characterization of the relevant allergens and therefore taking preventive measures to reduce exposure to environmental triggers [23].

Immunoglobulin E plays a pivotal role in allergic diseases, thus several reports have shown a link between the elevated total serum immunoglobulin E level and frequency of allergic diseases [24]. In the current study, the total serum IgE levels were elevated in 62% of sensitized cases. Likewise Chiu et al., found a strong correlation between total serum IgE and cosensitization of food and aeroallergens, these data provide remarkable evidence that elevated IgE levels triggered by various allergen sensitizations initiate severe allergic reaction and promote allergic diseases development [23]. However raised total IgE was not only correlated with allergy, but also may be found in a variety of clinical diseases, including certain primary immunodeficiencies, infections, inflammatory and parasitic diseases, therefore (sIgE) is a highly specific and reliable biomarker in the diagnosis of atopic diseases and in estimating their severity [7].

Regarding HDM, they are omnipresent in human settlements with propensity for humid environments such as tropical and subtropical zones and in several warm and moist regions of Saudi Arabia, particularly in Jeddah [25]. Many reports from different humid and hot areas delineated a high rate of mite's sensitization, for instance in Taiwan, Singapore, Malaysia and Thailand [23,26-28]. In consistency with these findings, we observed that *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* are the two commonly found indoor aeroallergens.
causing sensitization with 31.2 % and 30.9% prevalence rate respectively, followed by German cockroach 14.2% and cat dander 9.3%. Whilst, the most popular pollen allergens were Bermuda grass 7.7 % followed by Rye-grass 6.6 % and Timothy grass 6.1 %. These results were supported by a twin studies, one conducted in Taif city (KSA), while the other in Jeddah city, they concluded that the most frequent indoor aeroallergens were Dermatophagoides pteronyssinus followed by Dermatophagoides farina and American cockroach, taking into consideration that there are cross-reacting allergenic components between American and German cockroach species [29-31]. Furthermore, HDM sensitization is characteristic of most Asian atopic population. Statistics from many Asian countries have shown frequencies of more than 60%, even reaching up to 80% in allergic patients [5].

Pollen allergens are commonly encountered in subtropical or temperate zones in comparison to the tropics and it was noticeable that their ambient concentrations fluctuated all over the year according to their environmental seasons [32]. While in Taif city the most encountered pollen allergens were dessert palm pollen, Timothy grass and Rye grass, in that order, Alrabia results came to confirm that Bermuda grass is the most common pollen allergen in Jeddah city [29,30]. Another study covered various regions of KSA, United Arab Emirates and Sudan reported that the most frequent grass pollen was Bermuda grass with an average sensitization frequency of 19% overall the studied regions,which ranged from 3% in Jeddah to 31% in Riyadh (KSA) [33].The previous articles provides evidence that type of pollen allergens likely depends on the terrestrial and ecological distributions of trees and grasses in addition to seasonal variation. It is worth noting that there is a trend towards indoor and westernized lifestyle which in turn influencing the diversification and distribution of aeroallergens [5,34]. These reports could explain the difference in Najran (KSA) study which revealed that grass pollens, cat fur followed by dust mites were the most common allergens affecting young adults with prevalence of 20.8%, 18.9% and 12.7 % respectively [22]. Najran study also point out that allergen sensitization may vary across age groups and this has been clearly observed in our research through comparing total IgE level between different age groups and it came to light that young age groups recorded the highest level.

Molds found both indoors and outdoors, the most frequent indoor molds are Cladosporium, penicillium and Aspergillus. Mold tends to grow in places with a lot of moisture, thus in some warm and humid subtropical countries molds are pervasively present in homes [35]. In Taiwan, Cladosporium herbarum is the commonest species, while the most prevalent species detected in the present study was Candida albicans (7.1%) followed by Aspergillus fumigatus (4.5%) [23]. By way of comparison, Alrabia study demonstrated that Alternaria tenuis was the most frequent species with prevalence of 5.7%, then Cladosporium herbarum 4.3% and Candida albicans 2.9%, meanwhile among asthmatic individuals in Kuwait, Candida and Aspergillus species had a higher rate of reported sensitization (23% and 21%, respectively) [30,33].
The interplay of genetic, epigenetic and environmental factors may contribute to the disparity in common Food Allergy (FA) and paints a contrasting picture across countries worldwide. While crustacean and grains, are the most common FA of anaphylaxis in Korea, distinct differences in prevalence are observed in United States [36]. A single center study on adult onset FA in the United States reported the five most common food allergens as shellfish, tree nut, non-shell fish, soy and peanut [37]. These distinct differences in prevalence are observed even between countries located within the same continent. Nationwide Canadian survey implied that the main leading cause of adult FA was seafood, followed by fruits, vegetables and tree nut, in that sequence. [38,39]. These latter studies may account in part for our results regarding FA, the five most frequent causative FA were shrimp (16%), Cod fish (8.3%) and peanut (6%) followed by milk (5.7%) and Soyabean (5.2%). While the top five food allergens in Makkah city (KSA) were cocoa (27.5 %), peanuts (17.5%), egg white (15%), milk (12.5%) and strawberry (11.3%) [40].

Multiple scientific evidence has indicated the potential mechanisms by which vitamin D is involved in the pathogenesis of allergic diseases and its influence in the development of immune-mediated disorders [41]. It modulate the immune response which triggered by various allergens during the allergic inflammatory pathways by acting on vitamin D receptor expressed on many target cells, including B cells, T-cells, DCs and macrophages [42]. Thus vitamin D play a role in inhibiting inflammatory innate immune response, possibly by interfering with DCs differentiation from human monocytes, notably it was recorded that DCs differentiated in the presence of vitamin D had suppressed immunostimulatory capability [43-45]. Not to mention that, the effective form of vitamin D, 1,25-dihydroxyvitamin D3, may prevent skin infection by stimulating antimicrobial peptides expression like cathelicidin [46]. Likewise it has a detrimental effect on adaptive immune system particularly on T helper cell responses via inhibiting the generation of IFN-γ induced by IL-12 and the secretion of IL-4 and IL-13 as well [47]. Over and above it down regulates effector T-cell activity and inhibits T cell proliferation and IL-2 production. Furthermore, topical Vitamin D application has been observed to facilitate the induction and expansion of antigen-specific T regulatory cells, which use many inhibitory mechanisms including IL-10 and TGF-beta, alongside CTLA-4 and PD-1 surface molecules to control downstream effector functions that are associated with allergic diseases [48,49]. Principally, secreted IL-10 is required for suppressing improper Th2 mediated allergic immune responses and inflammatory pathologies [50,51]. On top of that, active vitamin D has a reported capacity to dampen Th17 cells differentiation, bioactivity and Th17-related cytokine production, inhibits the pathogenic function of B cells by stimulating apoptosis of activated B cells, preventing plasma cell differentiation and secretion of immunoglobulin including IgE secretion [52-55].

In the light of these findings, it has been attractive to assess whether blood levels of 25(OH) D were related to the frequency of allergic sensitization. We discovered a significant trend towards higher prevalence of hypovitaminosis D (74.7%) among sensitized patients, whose
25(OH) D values were less than 20 ng/ml and most of them had severe deficiency with a level even less than 10 ng/ml (56.6%). Moreover, our results revealed that patients with vitamin D deficiency are more vulnerable to have allergic sensitization to multiple allergens, both food and aeroallergens among all grades than those with insufficient or sufficient levels, especially in high reactivity group (grade 6) in which 95% of patients had vitamin D deficiency.

Many observational studies show results consistent to those we present. In Costa Rica a large cross-sectional study revealed that vitamin D insufficiency is relatively frequent in children with asthma and its levels were negatively associated with total serum IgE and markers of allergy [56]. Another study evaluated the link between 25(OH)D deficiency and sensitization to seventeen different allergens, it concluded that sensitization to eleven out of seventeen allergens was more prevalent in those with vitamin D deficiency when compared with insufficient or sufficient vitamin D levels in young age group [57].

A smaller study of approximately 70 children with and without asthma in Jeddah city also demonstrated that hypovitaminosis D is highly frequent amongst asthmatic children with marked significant increase in TNF-α as an indicator of asthma and allergy severity compared to healthy controls [58]. Similar works observing the role of vitamin D in asthma and allergies has been published formerly from different countries, most of them displayed a causal relationship between hypovitaminosis D and the development of allergies [59-61]. In contrast a recent retrospective study conducted in Riyadh city expressed deviated results, as it did not find any statistical difference in vitamin D levels between asthmatic patients who presented with anaphylaxis and their control group [62]. The reasons of these conflicting results may be attributed to small number of participants included in their study as vitamin D data was available for only 84 asthmatic patients. However, further work is necessary in order to provide more evidence and to catch clear whole picture.

**Conclusion**

Knowledge about allergen sensitization patterns in atopic diseases is crucial for establishing optimal preventive control and medical treatment measures. Reactivity of House Dust Mites, Cockroaches German, Cat dander and Bermuda grass were found to be the highest among aeroallergens in Jeddah city. Allergy from HDM is present in up to 62% of the sensitized patients, there is thus an imperative need for control measures to constrict HDM sensitization, meanwhile shrimp and fish allergies ranked highest among FA. Terrestrial and seasonal variations in aeroallergen sensitization have been identified even within the same country and changes in the trend of aeroallergen sensitization have been spotted throughout the year. The noticeable diversity in prevalence of allergic diseases among our patients in relation to vitamin D sufficiency suggests a beneficial role of vitamin D supplementation in preventing and managing allergy.


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