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Vitamin D levels and allergic diseases. An italian cross-sectional multicenter survey

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Key words

Vitamin D; allergic diseases; bronchial asthma; allergic rhinitis; atopic dermatitis; house dust mite; allergens

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Summary

Background. *During the two last decades, the interest in the role of Vitamin D (VD) in allergic disease has increased. Apart from the well-known actions of VD in bone metabolism, recent studies suggested its possible role as an immune-modulator in allergy.* ***Objective.*** *This study, conducted over the Italian territory, evaluated the possible correlations between VD serum level and diagnosed allergic diseases (rhinitis / asthma, food allergy, atopic dermatitis). Thus, VD was assessed in patients with physician-diagnosed allergic diseases.* ***Methods.*** *The study was carried out in hospital- and private practice-based setting between October 2012 and March 2013, and 18 Centers participated. Only adult patients, with at least one positive skin prick test were included. The diagnostic procedures and the data collection were standardized among the centers. VD levels were assayed by the same laboratory test.* ***Results****. Three hundred and nine patients were enrolled (132 male, mean age 37.5 ± 17 years). Of them, 40% reported a positive family history for allergies (asthma / rhinitis). Rhinitis plus asthma was present in 47% of patients, atopic dermatitis in 15%, and a consistent clinical history of food allergy associated with positive skin tests was present in 25% of subjects. There was no significant association between VD level and age, sex, family history, rhinitis, or food allergy. VD levels were overall lower in patients with asthma and rhinitis, but without statistical significance. A significant difference in VD levels was detected between patient with or without atopic dermatitis. VD was not related to seasonal allergens, whereas a significant negative correlation was seen for house dust mite and dog dander.* ***Conclusion****. Our data, derived from a cross-sectional study involving only allergic patients, agree partially with the current literature. Nonetheless, the association between VD levels and allergies appeared weak. Studies involving larger samples would be required to better define the association between VD and allergies.*

Introduction

During the two last decades, there was a renewed scientific interest in the Vitamin D (VD) system, since new observations suggested its functional role as an immunomodulator (including allergic diseases and asthma) (**1-4)**. Cholecalciferol, and its metabolites, are more properly hormones. Ultraviolet radiations determine, in the skin, the conversion of 7-dehydrocholesterol into cholecalciferol. Subsequently, liver enzymes hydroxylate it to 25-hydroxy-cholecalciferol, that is usually named and assayed as VD. The second hydroxylation, necessary for having an active hormone, occurs in kidney, where VD is converted in the active form (1-25 hydroxyVD, calcitriol) (5,6). Based on 25(OH) VD levels, subjects are categorized as: deficient (< 20 ng/mL), insufficient (≥ 20 and < 30 ng/mL), or sufficient (≥ 30 ng/mL). VD is well known to be essential for calcium resorption and bone metabolism in general. Apart this, VD seems to play also a relevant role in the general function / regulation of immune system, especially concerning lymphocyte activation, antigen receptor functioning and signaling pathways (7,8). On this background it was suggested that VD could affect the onset and course of allergic diseases and, may play therefore also a preventative role (9,10).

Indeed, in allergic diseases, the clinical studies so far available have provided conflicting results. In addition to serum levels of VD, other factors may play a crucial role in the development of allergies and asthma, including environmental and genetic factors. Also, the interventional studies with VD in patients with immune-mediated diseases did not provide conclusive results (11-13). The extent of involvement of vitamin VD-dependent and VD-independent pathways in homeostasis and regulation of immune system in diseases still needs to be explored. Some studies reported proofs of the role of VD in allergy. For this reason, we undertook a cross-sectional real-life study to evaluate if VD serum level is related to nature and severity of disease in patients with ascertained allergies.

Methods

The study was conducted in hospital- and private practice-based settings among Italian allergists between October 1st 2012 and March 30th 2013. Eighteen individual Centres participated in this survey, all adhering to AAITO (Italian Association of Territorial and Hospital Allergists). Each centre was required to collect demographic (age, sex familiar history etc.) and clinical data (severity and duration of symptoms) from at least 20 patients firstly referred for suspected allergic diseases, that had to be confirmed by the physicians themselves by the standard diagnostic procedures. Thus only diagnosis-naïve patients were included. The study was approved by, or simply notified to local ethic committees, as per Italian law, since the study was observational. Adult patients (> 18 years), with at least one positive skin prick test (see below) were included. Asthma and/or rhinitis were diagnosed according to current guidelines (14,15). Allergic rhinitis required the presence of nasal obstruction, sneezing, itching and rhinorrhea in various combinations, associated to concordant allergen exposure. Asthma was diagnosed on clinical basis and by functional respiratory tests. Atopic dermatitis was clinically diagnosed (distribution of lesions, history, onset) (16). Food allergy / sensitization diagnosis required, in addition to a suggestive clinical history, the positivity to commercial extracts and/or prick by prick with fresh food, and/or in selected cases to oral food challenge. For inhalant allergens a diagnostic panel of commercial standardized extracts was used in all Centres, including: mites (*Dermatophagoides pteronyssinus* and *farinae)*, grass mix, *Parietaria*, olive, birch, cypress, ragweed, cat/dog dander, *Alternaria*. Family history, demographic and clinical data were all included in a standardized database. Patients having concomitant systemic diseases, such as malignancies, celiac disease, autoimmune disorders or immunodeficit were not included. The serum level of VD was assayed at all centres by commercial ELISA kits, which limit of detection was 2 ng/mL. Samples were always run in duplicate with quality control samples to ensure the validity of results. This assay is regarded as the best representation of VD metabolic status, reflecting the total VD from dietary intake, sunlight exposure and conversion from adipose tissue in the liver.

Demographic variables were reported by descriptional analysis. VD levels were categorized within quartiles: 1: 1-14 ng/mL; 2: 15-22 ng/mL; 3: 23-36 ng/mL; 4: > 37 ng/mL (17). The categorization into quartiles was made to ease the interpretation of results regarding dichotomous outcome variables and to be able to directly compare odds ratios between highest and lowest levels of serum 25(OH)D. A multivariated logistic regression model was applied, with results expressed as Odds Ratio (OR) and confidence interval 95%. All analyses were two-tailed to reject the null hypothesis, with a threshold of $p = 0.05$. Statistical analyzes were performed using STATA software for personal computers (Stata Statistical Software 12.0, 2012; Stata Corporation, College Station, Texas, USA).

Results

Three hundred and nine patients (132 male, 177 female, mean age 37.5 ± 17.0 years) were assessed (**table 1**). Of them, 40% reported a positive family history for respiratory allergy (in one or both parents). Rhinitis was present in 84% patients and rhinitis plus asthma in 47%. Atopic dermatitis accounted for 15% of subjects, and food allergy / sensitization was diagnosed in 25% (32 patients, 20 of them with positive open food challenge). **Table 2** shows the distribution of patients according to VD level

Table 1 *- Demographic and clinical characteristics of the patients' population (n = 309).*

Sex, *n* (male/female)	132/177
Age years mean (SD)	37.5 ± 17.0
Positive atopy family history *n* (%)	128 (40%)
Residence: Urban/Rural	169/134
Allergic rhinitis *n* (%) *Mild* *Moderate-severe*	268 (84%) *81 (30%)* *187 (70%)*
Bronchial asthma alone *n* (%)	42 (13%)
Rhinitis plus asthma *n* (%)	151 (47%)
Atopic dermatitis *n* (%)	45 (15%)
Food allergy / sensitization *n* (%)	77 (25%)

Figure 1 *- Distribution of patients with bronchial asthma (left), allergic rhinitis (center) and atopic dermatitis (right) according to VD quartiles.*

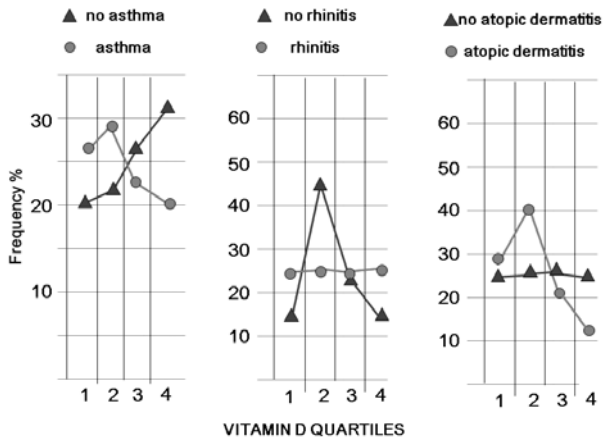
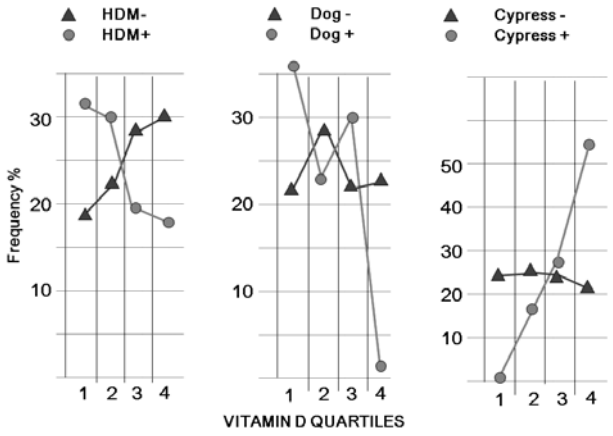


Figure 2 *- Distribution of patients with house dust mite sensitization (left), dog dander sensitization (center) and cypress sensitization (right) according to VD quartiles.*



quartiles in the population. There was no significant association between VD level, age, family history, rhinitis or food allergy (not shown). VD levels were overall lower in patients with asthma, but without statistical significance (p = .113) (**figure 1**), and the same was observed in patients with rhinitis (**figure 1**). A significant difference, according to VD levels, was detected between patient with or without atopic dermatitis (**figure 1**) (OR = 1.55, p = 0.042). VD level resulted to be not related to the sensitization to the most common seasonal allergens (grasses, *Parietaria*, olive, birch, not shown), except for cypress (OR = 0.36, p = 0.001) (**figure 2**). A significant inverse correlation was also seen for house dust mite (OR = 1.40, p = 0.005) and dog dander (OR = 1.49, p = 0.008) (**figure 2**). No difference was observed between the patients with VD < 20 ng/mL and those with higher serum concentrations according to their predominant clinical disease or sensitization. No statistical correlation could be detected even selecting those patients with ascertained food allergy (positive open oral challenge).

Table 2 *- Distribution of patients according to VD level quartiles (see text) in the population.*

Quartile	Q1	Q2	Q3	Q4	Total	P value
Age range						
18-29	27 (25.0%)	33 (30.8%)	24 (22.0%)	23 (21.5%)	107 (100%)	NS
30-49	30 (23.6%)	33 (25.9%)	29 (22.8%)	35 (27.5%)	127 (100%)	NS
50-76	19 (25.0%)	16 (21.0%)	23 (30.6%)	17 (22.6%)	75 (100.0%)	NS
Total	76	82	86	75	309	NS

Discussion

The data collected in the present study are only in part in agreement with the current literature. In fact, a positive / negative significant correlation between serum levels of VD and the presence of respiratory allergic disease could be not clearly demonstrated, and this was especially true for seasonal allergens. Indeed, our data would suggest some correlation between 25-hydroxyvitamin D levels and the immune response to perennial allergens, such as house dust mites and dog dander specifically. Our data remain partially in agreement with the results of previous studies (1,2,18). In particular, pediatric patients with asthma and allergic rhinitis and positive specific IgE to dust mite, had significantly lower VD levels than children with negative dust mites specific IgE (18). This would confirm a possible role of VD in the regulation of the immune system in allergies. On the other hand, our data cannot support the concept that VD might be useful as preventive treatment or as an adjunct to allergen immunotherapy as previously described (19,20,21), since this was not an interventional trial. The relatively small sample size could explain in part the weakness of correlations. Also, other potential confounding factors (e.g. time spent outside, type of allergic sensitization, physical exercise etc.) must be considered. Since those factors strictly interplay and overlap, it was not possible taking into account all of them, so that we opted for a more simplified and "clean" model.

Respiratory allergies such as asthma and allergic rhinitis, according to our study, did not show a significant correlation with low levels of serum 25-hydroxyvitamin D, although lower levels of VD in patients with asthma than non-asthmatics were noticed. This would be in agreement with the previously hypothesized role of VD in the development of innate and adaptive immunity, especially against infections (22). The present study demonstrated a significant difference between patients with or without atopic dermatitis, according to VD levels. It is also true that patients with atopic dermatitis have genetically-controlled risk factors that affect the barrier function. As the pathogenesis of atopic dermatitis involves a complex interplay of epidermal barrier dysfunction and dysregulated immune response, and VD is involved in both processes, it is reasonable to expect that VD levels could be associated with atopic dermatitis' risk or severity. This is in agreement to what shown in other studies (23-25). Of course, case-control studies comparing allergic and non-allergic subjects, and cross-comparing those with normal or low levels of VD are needed to identify significant differences. Of note, this study was not aimed at comparing healthy and diseased subjects, but at evaluating only patients with ascertained allergic diseases with regard to their VD serum level.

In conclusion, this study suggested that VD could have some role in atopic dermatitis and asthma, with a particular link with dust mite sensitization. Since most allergies start in childhood, VD deficiency or insufficiency in childhood might influence initiation of allergy targeting unclear and little known immunologic aspect of the disease (26).

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