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Prevalence of Vitamin D deficiency and associated factors in Mexican patients with allergic rhinitis and asthma

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Abstract

Introduction: *The general population has impaired serum Vitamin D (VD) levels. Poor values are associated with allergic diseases.* **Objective:** *The objective of the study was to determine the prevalence of VD deficiency and associated factors in patients with allergic rhinitis and asthma.* **Material and methods:** *This is a descriptive study in children 3-14 years old, with allergic rhinitis and asthma sensitized to aeroallergens identified by skin prick tests. We measured serum 25-hydroxy VD levels and evaluated associated factors.* **Results:** *Sixty-three patients were included, with a mean age of 7.25 years old, 54% were female. Mean weight was 26.7 kg, mean VD levels were 23.66 ng/ml (± 7.28), 22.2% had sufficient levels, 47.6% had insufficient levels, and 30.2% had deficient levels. We found an association with increased risk of VD deficiency in patients ages 12-14 years old (odds ratio [OR] 7.5, confidence interval [CI] 1.306-43.066), the skin type V with (OR 3.444, IC 2.334-5.083), and the lack of consumption of cod liver supplements (OR 1.475, CI 1.237-1.759).* **Conclusions**: *This sample of Mexican patients with allergic rhinitis and asthma showed the high prevalence of both VD deficiency and insufficiency. Consumption of cod liver supplements was a protective factor for deficiency. No association between VD deficiency and severity of allergic rhinitis and asthma was found in this sample of patients in the Mexican General Hospital of Mexico.*

Key words: Vitamin D deficiency. Asthma. Allergic rhinitis.

Introduction

Vitamin D (VD) has been described as an essential element in the maintenance of mineral homeostasis and bone architecture (X); however, the vision on the physiological functions of said nutrient has changed radically, the discovery of the VD receptor in immune system cells initiated a series of investigations related to the regulatory activity of this vitamin toward inflammatory phenomena and the association between low levels and development of various infectious and degenerative pathologies. Interest in VD has increased considerably because of multiple studies show that between 30 and 50% of the general population have serum VD deficiency[1,2]. In Mexico, Flores et al. report a prevalence of VD deficiency of 10-24% and 18-30% of insufficiency in children[3]. Ninety percent of VD requirements are synthesized through proper skin exposure to sunlight; the remaining 10% is obtained from food[4,5].

The main cause of VD deficiency is inadequate sunlight exposure. Sunscreen use reduces its synthesis more than 95%. People with dark skin tone require at least 3-5 times more sun exposure to produce the same amount of VD that a person with white skin tone. There is an inverse association with body mass index (BMI) because more than 30 kg/m^2 values are associated with deficiency. Other causes include malabsorption syndromes, nephrotic

syndrome (a case in which one loses VD bound proteins through urine), anticonvulsants, antiretrovirals, and chronic use of systemic corticosteroids[6]. Endocrinology guidelines for assessment, treatment, and prevention of deficiency suggest that 25 (OH) VD can be measured to evaluate blood levels of VD[6]. An optimal level is defined between 40 and 60 ng/ml, sufficiency between 30 and 39 ng/ml, insufficiency between 21 and 29 ng/ml, and deficiency < 20 ng/ml[7].

The association between VD levels and respiratory allergic diseases such as asthma and rhinitis has been investigated. Some studies have associated levels < 30 ng/ml with severe asthma, impaired lung function, frequent exacerbations, uncontrollable asthma, and increased use of inhaled steroids and oral steroids cycles in children, such effect implies a wear and tear both economically and in the quality of life[8]. Gupta et al. described VD insufficiency prevalence in 47% and deficiency in 17% of asthmatic patients[9]. Regarding allergic rhinitis, even though it shares similar inflammatory mechanisms with allergic asthma, its association with VD levels is less consistent[10,11].

The objective of this study was to evaluate the prevalence of VD deficiency in patients with respiratory allergies and describe the associated factors.

Material and methods

Study population

We conducted a transversal and descriptive study in patients between 3 and 14 years old who attended the allergy and immunology department, who had a recent clinical diagnosis of allergic rhinitis and asthma following ARIA and GINA guidelines. These patients were sensitized to one or more aeroallergen identified by a skin prick tests (Greer® allergens). As immunotherapy guidelines indicate, a positive skin prick test was considered if the wheal was 3 mm bigger than the negative control. All patients and their parents signed assent and informed consent. The protocol was approved by the Research and Ethics Committee of the Hospital (Approval number DI/6/309/04/013). This study was performed according to the Mexican General Health Law regarding Investigation in human beings and the Helsinki Declaration.

After a confirmed diagnosis of allergic rhinitis or asthma was made, we measured serum VD levels and we investigated the different variables considered to be related to VD levels. The following variables were evaluated: age, gender, BMI, type of birth, and season in which VD levels were taken, skin type according to

Table 1. General characteristics of the study population (n = 63)

Females n (%)	34 (54)
Age in years, mean (SD[a])	7 (IQR: 5-9)
Weight in kg, mean (SD)	23.05 (IQR: 19.8-34.5)
Body mass index (Kg/m²), mean (SD)	16.78 (± 2.76)
Vitamin D ng/ml, mean (SD) Sufficient levels (≥ 30) n (%) Insufficient levels (21-29) n (%) Deficient levels (< 20) n (%)	23.66 (± 7.28) 14 (22.2) 30 (47.6) 19 (30.2)
Total serum immunoglobulin E UI/l, mean (SD)	154 (IQR: 65.1-440)
Eosinophils, mean (SD)	230 (IQR: 200-500)

Type of birth, n (%)
  Cesarean section
  Vaginal delivery
	
	35 (55.6)
	28 (44.6)

Season, n (%)
  Winter
  Spring
  Autumn
	
	30 (47.6)
	30 (47.6)
	3 (4.8)

Skin type (According to Fitzpatrick) n (%)
  I
  II
  III
  IV
  V
	
	0
	2 (3.2)
	21 (33.3)
	39 (61.9)
	1 (1.6)

Sunscreen use, n (%)	17 (27)

Consumption of food rich in Vitamin D, n (%)
  Cod liver supplements
  Fish
  Mushrooms
  Egg
  Dairy products
  Cereals
	63 (100)
	4 (4.8)
	44 (69)
	9 (14.3)
	55 (87.3)
	61 (96.8)
	55 (87.3)

Allergic rhinitis n (%)
  Intermittent mild
  Intermittent moderate/severe
  Persistent mild
  Persistent moderate/severe
	63(100)
	18 (28.6)
	2 (3.2)
	6 (9.5)
	37 (58.7)

Asthma, n (%)
  Controlled
  Partially controlled
  Uncontrolled
	29 (46)
	5 (8.0)
	12 (19.0)
	12 (19.0)

Comorbidities n (%)
  Sinusitis
  Allergic conjunctivitis
  Atopic dermatitis
  Food allergy
	20 (32)
	10 (50)
	6 (30)
	3 (15)
	1 (5)

[a]Averages and standard deviation are shown; However, in the variables whose distributions were not normal, medians, and interquartile range are shown.

Fitzpatrick, time of sun exposure, sunscreen use, VD fortified food consumption, drugs that interfere with the metabolism and absorption of VD (systemic steroids,

Table 2. Patients characteristics according to Vitamin D values

Variables	Group I sufficient levels (≥ 30) (n = 14)	Group II insufficient levels (20-29) (n = 30)	Group III deficient levels (< 20) (n = 19)	p*
Age, n (%) 3-5 years old 6-11 years old 12-14 years old	5 (35.7) 8 (57.1) 1 (7.2)	11 (40) 17 (56.7) 1 (3.3)	2 (10.5) 12 (63.2) 5 (26.3)	0.032
Sex, n (%) Male Female	5 (35.7) 9 (64.3)	14 (46.7) 16 (53.3)	10 (52.6) 9 (47.4)	0.63
BMIa (Kg/m^2) medium (Minimun-maximun)	15.80 (13.52-21.66)	16.05 (13.22-20.98)	17.39 (12.77-26.19)	0.29
Type of birth, n (%) Caesarean section Normal	8 (57.1) 6 (42.9)	17 (56.7) 13 (43.3)	10 (52.6) 9 (47.4)	0.95
Season, n (%) Winter Spring Autumn	6(42.9) 7 (50) 1 (7.1)	14 (46.7) 15 (50) 1 (3.3)	10 (52.6) 8 (42.1) 1 5.3)	0.85
Skin Type, n (%) II III IV V	1 (7.1) 7 (50) 6 (42.9) 0	1 (3.3) 10 (33.3) 19 (63.4) 0	0 4 (21) 14 (73.7) 1 (5.3)	0.06
Using sunscreen n (%) Medium SPF 15-29 High SPF 30-50 Very high SPF > 50	3 (31.4) 0 0 3 (21.4)	9 (52.9) 3 (10) 4 (13.3) 2 (6.7)	5 (26.3) 1 (5.3) 2 (10.5) 2 (10.5)	0.83
IgE^b UI/ml, mean (SD)	304 (297.02)	360.64 (570.45)	460.57 (658.15)	0.57
Eosinophils, mean (SD)	392.85(350.85)	307.67(282.57)	455.26 (320.12)	0.23
Allergic rhinitis n (%) Intermittent mild Intermittent moderate/severe Persistent mild Persistent moderate/severe	4 (28.6) 1 (7.1) 2 (14.3) 7 (50)	8 (26.7) 1 (3.3) 0 21 (70)	6 (31.6) 0 4 (21.1) 9 (47.4)	1.0
Asthma, n (%) Controlled Partially controlled Uncontrolled	2 (14.3) 2 (14.3) 2 (14.3)	3 (10) 6 (20) 8 (26.7)	0 4 (21.1) 2 (10.5)	0.226
Comorbidities, n (%)	2 (14.3)	10 (33.3)	8 (42.1)	0.235

*p values were calculated using Kruskal–Wallis test, differences were considered statistically significant with p ≤ 0.05 Abbreviations: [a]Body mass index was estimated using the WHO Child Growth Standards, [b]Immunoglobulin E

anticonvulsants, and antiretrovirals), allergic rhinitis and asthma severity, associated diseases (Sinusitis, allergic conjunctivitis, atopic dermatitis, and food Allergy), total serum immunoglobulin E (IgE), peripheral blood eosinophil count, and 25 (OH) VD levels.

VD levels

VD levels were evaluated by the electrochemiluminescence method. Values were reported in ng/ml. Normal values were between 30 and 100 ng/ml. Patients were divided into three groups according to VD levels: ≥ 30 ng/ml sufficiency, 21-29 ng/ml insufficiency, and < 20 ng/ml deficiency.

Statistical analysis

It was performed with SPSS v. 24.0. For descriptive statistics of quantitative variables, mean, and standard deviation were used. For categorical variables, frequencies

and percentages were used. The mean comparison was performed using the Kruskal–Wallis test, and the Chi-square test was used for categorical variables. The odds ratio (OR) with confidence intervals (CI) of 95% with p < 0.05 was estimated.

Results

Demographic characteristics of the population

Sixty-three patients were included with a mean age of 7.25 years (± 2.84); 34 (54%) were females. The mean weight was 26.7 kg (± 10.89), mean BMI of 16.78 kg/m^2 (± 2.76), and VD mean levels of 23.66 ng/ml (±7.28), mean total serum IgE was 378.2 UI/mL (± 547.65), and eosinophils 371.1 cells/mL (± 311.6). Ninety-five percent of the samples were taken in winter and spring, and the skin type most commonly found was type IV in 61.9%. Twenty-seven percent of the population used some type of sunscreen. All the subjects consumed some food containing VD, milk being the most frequent.

According to inclusion criteria, all the patients had allergic rhinitis, 46% had asthma, and 32% had a concomitant disease. Of the patients with concomitant diseases, 50% had chronic rhinosinusitis, 30% had allergic conjunctivitis, 15% had atopic dermatitis, and 5% had food allergy, as described in table 1.

As shown in table 2, they were divided into three groups according to VD levels: 14 (22.2%) in Group I with sufficient levels (≥30), 30 (47.6 %) in Group II with insufficient levels (21-29), and 19 (30.2%) in Group III with deficient levels (< 20).

Table 2 describes each one of the groups' characteristics. VD values show that the patients in Group III had higher BMI values, total serum IgE, and eosinophils. Group III also had more comorbidities, but only observing statistically significant differences in the age and skin type.

Table 3 divides the population into the following categories based on VD enriched food consumption: no consumption versus consumption. Cod liver supplement consumption was common in five patients who had higher VD levels. Table 4 describes the frequency of sun exposure in minutes per day. No statistically significant differences between the groups were observed.

Reason of mummies associated of VD deficiency and insufficiency

We found that 47.6% of patients had insufficient VD levels, while 30.15% had deficient levels, according to the classification mentioned previously.

Table 3. Vitamin D rich foods consumed, n (%)

Variables	Group I (n = 14)	Group II (n = 30)	Group III (n = 19)	p*
Cod liver supplements				0.02
No	11 (78.6)	29 (96.7)	29 (96.7)	
Yes	3 (21.4)	1 (3.3)	1 (3.3)	
Fish				0.23
No	2 (14.3)	9 (30)	8 (42.1)	
Yes	12 (85.7)	21 (70)	11 (57.9)	
Mushrooms				0.56
No	12 (85.7)	27 (90)	15 (78.9)	
Yes	2 (14.3)	3 (10)	4 (21.1)	
Egg				0.94
No	2 (14.3)	4 (13.3)	2 (10.5)	
Yes	12 (85.7)	26 (86.7)	17 (89.5)	
Dairy products				0.69
No	0	1 (3.3)	1 (5.3)	
Yes	14 (100)	29 (96.7)	18 (94.7)	
Cereals				0.27
No	0	5 (16.7)	3 (15.8)	
Yes	14 (100)	25 (83.3)	16 (84.2)	

*The differences were considered statistically significant with p ≤ 0.05, these P values were calculated using the Chi-square test.

RISK FACTORS ASSOCIATED WITH VD DEFICIENCY

The only group that showed a lower risk of VD deficiencies was 3-5 years old (OR 0.18, 95% IC 0.03-0.91). However, it can be recognized that patients at risk of VD deficiency were those aged 12-14 years old (OR 7.5, 95% IC 1.306-43.066), those with skin type V (OR 3.444, IC 2.334-5.083 95%, P 0.125), moderate-severe intermittent rhinitis (OR 1.452, 95% IC 1.227-1.719), and controlled asthma (OR 1.487, 95% CI 1.243-1.780). The lack of consumption of cod liver supplements was associated with deficiency (OR 1.475, 95% CI 1.237-1.759, p: 0.1), table 5.

We did not find other conditions associated with low levels of VD in any of the patients, such as the use of systemic corticosteroids, antiretrovirals, anticonvulsants, or protein-losing syndromes.

Discussion

This study shows a VD deficiency of 30.15%, and insufficiency of 47.1%, indicating that only 22.75% of the study population has sufficient VD levels. These data are superior to those showed by the national health and nutrition survey (ENSANUT) 2006 that reported a VD deficiency of 24.1% and insufficient of 30% in children between 2 and 5 years old, and a deficiency

Table 4. Sun exposure (minutes/day)

Variables (min)	Group I sufficient levels (≥ 30) (n = 14)	Group II insufficient levels (21-29) (n = 30)	Group III deficient levels (< 20) (n = 19)	p*
0-15	2 (14.3)	4 (13.3)	0	0.24
16-30	2 (14.3)	1 (3.3)	2 (10.5)	0.60
31-45	1 (7.1)	0	1 (5.3)	0.12
46-60	1 (7.1)	6 (20)	2 (10.5)	0.55
61-75	0	1 (3.3)	1 (5.3)	0.69
76-90	1 (7.1)	0	0	0.17
91-105	1 (7.1)	0	0	0.17
106-120	1 (7.1)	5 (16.3)	7 (36.8)	0.19
> 120	5 (35.7)	13 (43.3)	6 (31.6)	0.70

*p values were calculated using Kruskal–Wallis test, differences were considered statistically significant with p ≤ 0.05.

of 10% and insufficiency of 18% in children between 6 and 12 years old. This survey was conducted in the general population, unlike our study that included only allergic patients. We found that patients between 12 and 14 years old showed an increased risk of deficiency, unlike the ENSANUT survey, which reported a higher deficiency in the preschool group[3]. BMI was higher in the group of patients with deficiency, but there was no statistically significant difference between the groups and no association, unlike what is reported in the literature, in which it is stated that patients with a higher BMI have lower VD levels. There are different hypotheses that explain deficiency in these subjects such as low sun exposure, poor supplement intake, accumulation into adipose tissue, or more bone mass needed to support the heavy weight[12].

The season in which VD levels were measures does not show significant differences between groups, and no risk of significant association was found, despite what Webb et al. report, as they observed lower VD levels in the winter months caused by differences in solar radiation during those months. Although, this study was carried out in a Canadian population where solar exposure may be lower in the winter months than in our population[13].

Significant association was found in types II and V according to Fitzpatrick being greater in the latter. However, we did not explain why skin types being these extremes were associated with the deficiency, different from what Clemens et al. who describe that higher levels of melanin are associated with lower levels of VD due to a decrease in solar absorption in hyper-pigmented skin[14].

Regarding the use of sunscreen, a greater association with deficiency was found with its use, but the OR did not show a statistically significant association. Matsuoka et al. described that using a sunscreen with a sun protection factor > 15 decreases VD absorption in the skin up to 99%[15].

Higher levels of IgE and eosinophils were found in patients with VD deficiency, but the OR did not show a significant association. Muehleisen describes the role of VD in the regulation of IgE production, which may explain that low levels of VD produce an imbalance of regulatory T cells and IgE-producing B cells. However, other authors have not been able to find this association[16].

Regarding the association with allergic rhinitis, there are controversial data some authors have documented a strong relationship between levels of VD and allergic process, for example: Vasallo and Camargo demonstrated that VD deficiencies are associated with low tolerance to environmental allergens[17]. On the other hand, Mai et al. documented that in adult Norwegian patients there is a significant relationship between deficient levels of VD and the development of allergic rhinitis[18]. Rothers et al. found that deficient levels of VD in umbilical cord blood are associated with aeroallergens and predispose to the development of rhinitis and asthma and even Gupta et al. described that low levels of this vitamin are associated with severe asthma, uncontrolled disease, and airway remodeling[19,20]. By another hand, others researchers found no significative associations between rhinitis and lower levels of VD[8]. In our case, those patients with persistent disease were associated with the lower VD values without statistical significance, so we

Table 5. Association between patients characteristics and Vitamin D status

Variable	OR	95% IC	p‡
Age, n (%)			
3-5 years old	0.18	0.03-0.91	0.02
6-11 years old	1.30	0.43-3.94	0.63
12-14 years old	7.50	1.30-43.06	0.03
Sex			
Male	1.46	0.49-4.30	0.49
Female	0.68	0.23-2.01	0.49
Body mass index percentile			
Under weight	0.91	0.16-5.20	0.92
Normal	0.71	0.23-2.23	0.56
Overweight	0.91	0.16-5.20	0.92
Obesity	0.91	0.16-5.20	0.92
Type of birth, n (%)			
Caesarean section	1.11	0.40-3.48	0.75
Vaginal delivery	0.84	0.28-2.48	0.75
Season, n (%)			
Winter	1.33	0.45-3.92	0.60
Spring	0.72	0.24-2.15	0.56
Autumn	1.16	0.09-13.69	0.90
Skin type			
II	1.45	1.22-1.71	0.35
III	0.42	0.12-1.49	0.17
IV	2.12	0.65-6.94	0.20
V	3.44	2.33-5.08	0.12
Sunscreen use	1.05	0.31-3.54	0.93
Immunoglobulin E (UI/l)			
0-165	0.55	0.17-1.72	0.45
≥166	1.80	0.58-5.61	0.30
Eosinophils			
0-300	0.46	0.15-1.39	0.16
≥300	2.14	0.71-6.42	0.16
Allergic rhinitis n (%)			
Intermittent mild	1.23	0.38-3.97	0.72
Intermittent moderate/severe	1.45	1.22-1.71	0.34
Persistent mild	5.60	0.92-33.77	0.04
Persistent moderate/severe	0.51	0.17-1.53	0.22
Asthma, n (%)			
Controlled	1.48	1.24-1.78	0.12
Partially controlled	1.20	0.31-4.59	0.79
Uncontrolled	0.40	0.07-2.03	0.25
Comorbidities	1.93	0.62-5.98	0.24
Cod liver supplements			
No	1.47	1.23-1.75	0.17
Yes	0.67	0.56-0.80	0.17
Sun exposure			
< 60 min	0.56	0.17-1.86	0.34
61-120 min	2.82	0.87-9.10	0.07
Over 120 min	0.66	0.21-2.08	0.48

Odds Ratio (OR), confidence interval (CI), ‡differences were considered statistically significant with p ≤ 0.05, p values were calculated using the Chi-square test.

cannot establish a proper association between rhinitis severity and VD deficiency. We did not find an association between VD deficiency and asthma severity and in similar way, VD deficiency seems to be associated with higher comorbidities, such as rhinosinusitis[21]. However, we did not find a statistically significant association.

With respect to foods enriched with VD, we found that cod liver supplement consumption is a protective factor for deficiency, which is due to its high content of this vitamin[22]. Holick et al. described that exposure to sunlight is a protective factor for VD deficiency, but we were unable to demonstrate this association[6].

This study has some limiting, including a small sample size and that it only included children. We could not find a strong association with some variables considered to be important regarding VD levels, but this could have been more evident with a bigger sample. One of problem in this work is that it only included allergic patients so we have an idea of VD deficiency repercussion in this population but the comparison is not complete without a control group. In the future, it could be convenient to include a control group to establish if this condition is related to the allergic conditions in these patients.

VD deficiency is a global public health problem, and patients with allergic rhinitis and asthma show a high either deficiency or insufficiency – even more than the general population. Different studies have shown an association between VD deficiency and severe manifestations of allergic diseases. However, we could not demonstrate that relationship with statistical significance. It seems that consumption of cod liver supplements is a protective factor for deficiency.

The deficiency of VD is high in allergic patients; the factors associated with the deficiency were little consumption of cod liver, age, skin photo type, and moderate-severe rhinitis. It is necessary more works to confirm our findings and to reveal the mechanisms underlying these observations.

Conclusions

Vitamin D deficiency is frequent in allergic patients due to several factors such as cod liver consumption, age, skin phototype and the presence of moderate-severe allergic rhinitis.

There is a need for similar studies, not only to confirm our findings, but also, those investigating the underlying mechanism by which allergic patients have lower vitamin D levels compared to the rest of the population.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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