



# Vitamin D Levels in Patients with Allergic and Non-Allergic Rhinitis

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## ABSTRACT

**Objective:** Allergic and non-allergic rhinitis are quite similar from a clinical viewpoint and allergen sensitivity seems to be the important relevant difference between them. However, the role of vitamin-D (vit-D) as an immunomodulator hormone and on rhinitis phenotypes is not clear. We aimed to investigate the relation between vit-D levels and patients with rhinitis as allergic (AR) and non- allergic (NAR).

**Materials and Methods:** This was a retrospective research of 228 patients whom were diagnosed at a tertiary hospital between 2012 and 2016. Rhinitis was diagnosed as AR if nasal symptoms were accompanied with skin prick test (SPT) positivity, and NAR if they were relevant with negative SPT. The clinical history of the patients and the symptoms were recorded. Serum total IgE tests were performed using an allergen detection system (UniCAP, Phadia, Uppsala, Sweden), and vit-D levels were measured with the 25-hydroxy-vit-D (25-OH vit-D) kit in the Elecsys 2010 analyzer (Roche Diagnostics, Germany).

**Results:** A total of 228 patients (AR=170 and NAR=58) with a mean age of 31.06±11.58 yrs were included. The mean age and ratio of female gender were significantly higher in NAR (p=0.03), whereas obesity was significantly higher in AR patients (p=0.01). Duration of rhinitis in NAR was longer than in AR (p=NS). Serum total IgE levels were significantly higher in AR than NAR, whereas mean levels and ratio of vit-D deficiency were similar between the groups. Levels of vit-D were significantly lower in females than males only in the AR group (p<0.001). Patients with NAR had mostly severe vit-D deficiency (<10 ng/mL), and those with AR had mostly non-severe vit-D deficiency (11-19 ng/mL). There was no relationship between vit-D deficiency and allergen sensitization, but there was a negative correlation of vit-D levels and female gender in the AR group (p<0.001).

**Conclusion:** The present study showed no association between serum vit-D level and allergen sensitization in adult patients with allergic and nonallergic rhinitis.

**Keywords:** Allergic rhinitis, non-allergic rhinitis, allergic diseases, allergen sensitization, vitamin-D deficiency

## INTRODUCTION

Allergic rhinitis (AR) is an inflammatory disorder caused by immunoglobulin E (IgE)-related inflammation of the nasal mucosa due to various inhaled allergens (pollens, house dust mites, and molds). The common symptoms of AR are rhinorrhea, sneezing, nasal blockage, and itching of the nose. The prevalence of AR varies between 10% and 30% of the population due to geographical and aeroallergenic differences, and more than 500 million people worldwide are affected (1). Even though AR is not a life threatening disease, it can significantly impact the

quality of life. Thus, it is important to evaluate the risks in the development of AR such as genetic and environmental factors (1). Recently, vitamin-D (vit-D) was reported to play a role in the pathogenesis of allergic diseases.

Vit- D is an essential fat-soluble vitamin that can be obtained from the food, as well as by exposure to sunlight. Active vit-D has many functions in the immune system. Receptors of the active form of 1,25-dihydroxyvitamin D3 (1,25-OH<sub>2</sub> vit-D<sub>3</sub>) have been found in parts of immune system as well as in dendritic cells, monocytes, macrophages, and lymphocytes (2). The vitamin is related to lymphocyte

activation, and plays an important role in regulating general functions in antigen receptor functioning and signaling pathways (3-4). As vit-D is related to the immune system, its deficiency increases the tendency to allergic diseases (5,6). Sharief et al. have shown that vit-D deficiency was associated with higher levels of IgE sensitization in 3136 children and 3454 adults in a one-year survey (7). Wjst and Hypponen have found an increased prevalence of allergic rhinitis in 18.224 patients with vit-D deficiency (8).

The rationale to analyze serum vitamin D levels in patients with rhinitis was that rhinitis is not a disease with an impact on vit-D serum levels or metabolism but vit-D deficiency is related to an increased tendency to allergic diseases. In this study, we aimed to determine whether 25-OH vit-D levels were associated with rhinitis in an adult Turkish population and to investigate the effect of 25-OH vit-D levels on allergen mono or polysensitization in allergic patients.

## MATERIALS and METHODS

A total of 228 patients with rhinitis (nAR=170 nNAR=58) who presented to the Immunology and Allergy outpatient clinic of Kirikkale University Hospital between 2012 and 2016 were retrospectively examined. We obtained ethical board approval for the research. The data of patients were obtained from the hospital information management system. Adult patients were included if they had rhinitis with or without asthma, allergy tests (SPT and/or serum specific IgE), and serum 25-OH Vit D levels. The patients' history and the medications they used were noted from national electronic system. Patients with comorbidity or those using medications that might affect serum vit-D levels were excluded, as well as files with missing data.

Demographic data such as age, gender, and body mass index (BMI; kg/m<sup>2</sup>) were collected. Allergic rhinitis was described as a positive skin prick test (SPT) or specific IgE (speIgE) with nasal symptoms, whereas the patients diagnosed with NAR had negative SPTs/speIgE.

Allergen extracts from well-known manufacturers were used for SPTs (ALK, Milan, Italy). The test was performed with frequent allergens (Dermatophagoides farina and pteronyssinus, cat, dog, cockroach, mix trees, mix grasses, molds and latex). In addition to these extracts, negative and positive controls were also performed. If the diameter of the wheal was 3 mm or more the test result was considered as positive.

We used Unicap 100 with the fluoroimmunoassay technique (Phadia, Uppsala, Sweden) to measure total IgE and specific IgE levels. The electrochemiluminescence technique on the Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany) was used for plasma vit-D levels in our laboratory. 25-OH vit-D levels were classified into five groups as normal (>30 ng/mL), insufficiency (20-30 ng/mL), and deficiency (11-19 ng/mL) (1). We also subgrouped deficiencies as severe deficiency (5-10 ng/mL), and very severe deficiency (<5 ng/mL).

Statistics were analysed with the SPSS 20 software (IBM SPSS Inc, Chicago, Illinois, USA). In addition to descriptive statistics (median, standard deviation), we used the Independent-Samples T-Test to compare the quantitative data for normally distributed parameters. The chi-square test was used to compare two independent qualitative data. The Kolmogorov-Smirnov test was performed to test whether the distribution was normal. When the data did not have a normal distribution, the Mann-Whitney U test was used to compare independent groups. The significance level was set at  $p < 0.001$  and  $p < 0.05$ .

## RESULTS

Two hundred twenty eight patients with rhinitis were grouped as AR and NAR (Table I). The AR group consisted of 170 patients (M/F; 62/108, age; 15-69 years with a mean  $31.06 \pm 11.58$  years), whereas the NAR group consisted of 58 patients (M/F; 9/49, age; 15-63 years, mean;  $35.21 \pm 13.66$  years). The mean age and the number of females were significantly higher in the NAR group ( $p = 0.03$ ). Although the BMI of the two groups were similar, the ratio of obesity was significantly higher in patients with AR compared to NAR ( $p = 0.01$ ). The overall duration of rhinitis was  $6.22 \pm 0.35$  years, but in patients with NAR it was insignificantly higher. Serum total IgE levels were significantly higher in AR than NAR, whereas mean levels and ratio of vit-D deficiency were similar between the two groups. Almost all of the group had lower 25-OH vit-D levels (<30 ng/ml) (AR 96.4%, NAR: 93.1%). The most common severity level was severe 25-OH vit-D deficiency (5-10 ng/ml) in NAR, but deficiency (11-19 ng/ml) in AR (Table II). The level of 25(OH) vit-D was significantly lower in females than males ( $12.2 \pm 7.8$  ng/ml,  $17.1 \pm 8.9$  ng/ml, respectively) in the AR but not in the NAR group ( $p < 0.001$ ). There was no correlation between vit-D levels with age, total IgE level, duration of rhinitis, or BMI (results not shown). A significant association was found with female gender in AR ( $r = 0.280$ ,  $p < 0.001$ ).

**Table I: General characteristics of the study groups.**

n (%)	Total (n=228)	AR (n=170)	NAR (n=58)	p value
Age (yrs)*	32.11±12.24	31.06±11.58	35.21±13.66	0.03
Gender F/M	167/61 (73.2/26.8)	108/62 (63.5/37.5)	49/9 (84.5/15.5)	0.03
BMI (kg/m <sup>2</sup> )*	24.70±4.39	24.82±4.42	24.33±4.34	0.46
Obesity ratio	92 (40.4)	77 (45.3)	15 (25.9)	0.01
Duration of rhinitis (yr)*	6.22±0.35	5.94±0.34	7.03±0.93	0.52
Total IgE**	61.05 (28.9-165.25)	70.75 (34.55-178.50)	37.35 (19.17-143.75)	0.03
Vitamin D*	14.01±8.55	13.71±8.29	1.86±9.28	0.37

\*: mean ± standard deviation, \*\*: median (minimum-maximum).

**Table II: Vitamin D status in NAR, mono- or polysensitized AR, and in various sensitizations.**

n (%)	Total (n=228)	Very severe deficiency (<5 ng/ml)	Severe deficiency (5-10 ng/ml)	Deficiency (11-19 ng/ml)	Insufficiency (20-30 ng/ml)	Normal (30-50 ng/ml)
<b>NAR</b>	58 (25.43)	4 (6.9)	21 (36.2)	17 (29.3)	12 (20.7)	4 (6.9)
<b>AR</b>	170 (74.57)	21 (12.35)	41 (24.11)	76 (44.7)	26 (15.29)	6 (3.52)
<b>Monosensitized</b>	138 (81.1)	13 (13)	37 (26.8)	53 (38.4)	25 (18.1)	5 (3.6)
<b>Polysensitized</b>	32 (18.8)	3 (9.4)	4 (12.5)	23 (71.9)	1 (3.1)	1 (3.1)
<b>Pollens</b>	130 (76.4)	14 (10.7)	28 (21.5)	61 (46.9)	22 (16.9)	5 (3.8)
<b>HDM</b>	55 (32.3)	10 (18.2)	13 (23.6)	26 (47.3)	5 (9.1)	1 (1.8)
<b>Blatella</b>	23 (13.5)	5 (21.7)	4 (17.4)	11 (47.8)	2 (8.7)	1 (4.3)
<b>Cat/Dog</b>	15 (8.8)	1 (6.7)	4 (33.3)	7 (46.7)	2 (13.3)	-
<b>Mold</b>	9 (5.2)	-	2 (22.2)	6 (66.7)	1(11.1)	-
<b>Latex</b>	2 (1.17)	-	1 (50)	1 (50)	-	-

Most of the AR patients were monosensitized, whereas 18.8% of them were polysensitized. Common allergen sensitizations of the AR group were pollens followed by house dust mites, blatella, cat-dog, mould, and latex. Vit-D deficiency was not related to allergen sensitization, as vit-D status was mostly deficient in all sensitizations, except latex.

## DISCUSSION

In vivo and in vitro studies have found that vit-D has a wide spectrum of effects on the immune system (9). However, the place of vit-D in the etiology of allergic diseases is unclear, as previous studies did not show a definite relationship between allergic rhinitis/allergic susceptibility and 25-OH vit-D levels. In a recent publication by Feng et al, the Mendelian randomization (MR) study has no evidence of a causal relationship between serum vit-D level and AR risk and allergic susceptibility, suggesting that vit-D supplementation may not be effective in preventing allergy (10).

There are conflicting results about the mechanisms between vit-D and AR (9). Vit-D was determined to reduce AR-associated inflammation, inhibit the proliferation of T cells, and promote the development of regulatory T cells and transcription of Th17 cells, inducing an anti-AR effect. It has also been shown to have a pro-AR effect and induce Th1 to Th2 transition and increase Th2 cell development and response (11-13). We think that the balance between anti-AR and pro-AR effects determine the clinical course of the allergic patients.

In our study, 25-OH vit-D levels were the same between AR and NAR. Although serum 25-OH vit-D levels were below the cut-off value defined as vit-D deficiency (<30 ng/ml) in 95.6% of the study group, AR deficiency was observed in patients with vit-D levels. More frequent (11-19 ng/ml) and more severe deficiency was found in NAR (5-10 ng/ml).

Vit-D deficiency/insufficiency is common in the world. Turkey is one country where vitamin-D deficiency is endemic. Solak et al. analyzed the data of 35,667 persons and showed that the serum 25-OH vit-D level was below 30 ng/mL in 94.47% of the individuals participating in the study (14). Consistent with the high prevalence of vit-D deficiency in the general population, it can be assumed that our results are extremely reliable.

We found some differences between AR and NAR such as the female gender was insignificantly higher in the NAR group, and the ratio of obesity and serum total IgE was significantly higher in patients with AR. Although the majority of the patients in both groups were female, gender distribution was not different between the patients with allergic and non-allergic rhinitis, similar to our previous study (15). 25-OH vit-D levels did not correlate with age, total IgE, disease duration, or BMI. However, they were found to be significantly associated with female gender only in the AR and not in the NAR group ( $r=0.280$ ,  $p<0.001$ ). In our study, although the mean serum 25-OH vit-D level was lower in females than in males, this was significant only in patients with AR. The difference in serum 25-OH vit-D levels between genders may not be due to hormonal reasons, but indoor sedentary lifestyle that affects sunlight exposure. This high prevalence of low vitamin D status may be associated with less vitamin D synthesis in response to ultraviolet B (UVB), in individuals with high skin melanin content or due to aging and the use of extensive skin coverage, as well as scarce exposure to sunlight (16). The reason of high prevalence of vit-D deficiency in the female population of Turkey may be related with fact that the working population in our country is mostly men, while women spend most of the day at home, resulting in low exposure to vit-D. Furthermore, the lower level of vit-D in females may also be related to the traditional clothing style with increased age.

In the present study, although patients showing sensitisation with pollens had the lowest ( $13.6\pm 8.6$  ng/ml), and those with HDM had the highest ( $14.7\pm 8.9$  ng/ml) vit-D levels, none of the sensitisation profiles showed a significant difference. Moreover, we did not find any association between allergen mono-polisensitization and vit-D levels. Consistent with our results, large cross-sectional studies of adults in the United States also showed no association (7,8). Likewise, a systematic review and meta-analysis of vit-D status was performed to investigate

the association with allergen sensitization and AR (17). Although the authors had observed a lower prevalence of AR in individuals with high serum vit-D levels, this association was mainly observed in adult men. In a study performed in children, low serum vit-D levels were not only found in AR and in AR with asthma, but were also significantly associated with allergic sensitization to mites (18).

To our knowledge, this is one of the few studies to evaluate the vit-D status in patients with nonallergic as well as allergic rhinitis. The only investigation in patients with NAR was the mendelian randomization study focusing also on AR, and did not find any association with vit-D, similar to our results (10). We analyzed vit-D levels in patients with rhinitis, since rhinitis was not a disease to interfere with vit-D metabolism, and vit-D was shown to have an effect on allergic diseases. On the other hand, the indications of vit-D analysis in patients varies in the records, i.e. patients' request, symptoms, and clinical suspicion of vitamin deficiency according to symptoms, but is mostly not stated.

The main limitation of this study was its' retrospective design and female predominance, as well as the very low vit-D levels in our country. Excluding patients with comorbid diseases affecting vit-D levels might have caused a bias in this study, but proper randomisation could not be achieved in retrospective studies. However, we ensured that the selected subgroups were equivalent to the population as almost two thirds of the rhinitis population had AR and the rest had NAR (15). Another limitation was the absence of a control group that weakened the results, but it was difficult to find healthy controls in retrospective analyses. Furthermore, the data were limited with the recorded information, as we did not know the participants' life style conditions such as dietary habits, sun exposure, and frequency of hijab clothing. Variations in sun exposure depending on latitude, season of vit-D assay, atmospheric components, clothing style, use of sunscreen and skin pigmentation, and the prevalence of age, obesity and various chronic diseases affect vitamin D levels (19).

Previously, it was suggested that vit-D deficiency had an affect on upper airways with no relation to mechanistic link. However, in this study, there was no association between allergen sensitization and vit-D levels, contrary to reports that have found that vit-D might have a negative effect on allergic diseases (7,8,17).

In conclusion, vit-D deficiency/insufficiency is widespread in Turkey. AR and NAR are quite similar from a clinical viewpoint and allergen sensitivity still remains the only relevant difference. Even though vit-D is assumed to have immunomodulatory effects, the main finding of the study is the similarity of the mean levels of serum vitamin D and ratio of vit-D deficiency between allergic and nonallergic rhinitis groups. Further prospective studies involving more patients are needed to determine the precise role of vit-D in the pathogenesis of rhinitis of various etiologies.

#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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#### Authorship Contributions

Concept: **Merve Poyraz**, Design: **Ayse Baccioglu**, Data collection or processing: **Betul Dumanoglu**, Analysis or Interpretation: **Ayse Fusun Kalpaklioglu**, Literature search: **Gulistan Alpagat**, Writing: **Gulistan Alpagat**, Approval: **Sumeyra Alan Yalim**.

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