

The Relationship between Th1/Th2 Balance and 1α , 25-Dihydroxyvitamin D₃ in Patients with Allergic Rhinitis

Alerjik Rinitli Hastalarda Th1/Th2 Dengesi ile 1α , 25-Dihidroksivitamin D₃ Arasındaki İlişki

Original Investigation
Özgün Araştırma

Erol Keleş¹, Şule Özkar¹, Nevin İlhan², Hilal Güngör², Turgut Karlıdağ¹, Şinasi Yalçın¹

¹Department of Otorhinolaryngology, Fırat University School of Medicine, Elazığ, Turkey

²Department of Biochemistry, Fırat University School of Medicine, Elazığ, Turkey

Abstract

Objective: With regard to the correlation between T helper1/T helper2 (Th1/Th2) cell balance and 1α ,25-dihydroxyvitamin D₃, active metabolite of vitamin D, we studied Th1/Th2 cell balance by measuring levels of the cytokines interleukin (IL)-4, IL-10 and interferon-gamma (IFN- γ), which are important for immune response of patients with allergic rhinitis.

Methods: Thirty adult patients diagnosed with allergic rhinitis (study group) and 40 healthy volunteers (control group) are examined in the research. IFN- γ , IL-4, IL-10, and total immunoglobulin E (IgE) levels from serum samples and vitamin D₃ levels from plasma were determined in all patients.

Results: In IgE, IL-4, IL-10, IFN- γ , and 1α ,25-dihydroxyvitamin D₃ levels (p<0.05), a statistically noticeable difference was observed between the study and control group. The 1α ,25-dihydroxyvitamin D₃ levels in both groups were compared and a statistically significant dif-

ference between the 1α ,25-dihydroxyvitamin D₃ levels in the study group and that in the control group (p<0.05) was observed. There was a positive correlation between IFN- γ and vitamin D levels (p<0.05) in the study group, whereas IgE, IL-4, and IL-10 levels showed a negative correlation with vitamin D₃ levels (p<0.05).

Conclusion: In our study, 1α ,25-dihydroxyvitamin D₃ levels were associated with Th1/Th2 balance in allergic rhinitis, and a remarkable correlation was observed among vitamin D deficiency and allergy. These findings show that 1α ,25-dihydroxyvitamin D₃ may have a remarkable role in the severity and control of allergic disorders. In addition, further investigations are required to confirm how vitamin D should be used in allergic diseases. Furthermore, to reveal the exact mechanism of vitamin D on allergic diseases, further studies are required.

Keywords: Rhinitis, allergic, cholecalciferol, Th1 cells, Th2 cells, interleukin-4, interleukin-10, interferon-gamma

Özet

Amaç: Bu çalışmada alerjik rinitli olan hastalarda immün yanıtta rol oynayan İnterlökin-4 (IL-4), İnterlökin-10 (IL-10) ve İnterferon-gamma (IFN- γ) sitokinlerinin düzeylerini belirleyerek T helper 1/T helper 2 (Th1/Th2) hücre dengesininin araştırılması ve bu denge ile D vitamininin aktif metaboliti olan 1α ,25-dihidroksivitamin D₃ arasındaki ilişkinin belirlenmesi amaçlandı.

Yöntemler: Çalışma alerjik rinitli olan 30 erişkin hasta (çalışma grubu) ve 40 sağlıklı gönüllü (kontrol grubu) üzerinde yapıldı. Bütün hastaların ve kontrol grubunun serum örneklerinde IFN- γ , IL-4, IL-10 ve total İmmünglobulin E (IgE) seviyeleri, plazma örneklerinde ise D vitamini düzeyleri ölçüldü.

Bulgular: Çalışma ve kontrol grubu kıyaslandığında; IgE, IL-4, IL-10, IFN- γ ve D vitamini değerleri arasında istatistiksel olarak anlamlı bir farklılık tespit edildi (p<0.05). Her iki grup vitamin D değerleri açısından kıyaslandığında istatistiksel olarak anlamlı bir farklılık saptandı (p<0.05). Grup İde; IgE, IL-4, IL-10 değerleri ile D vitamini değerleri arasında negatif yönde; IFN- γ değerleri ile D vitamini değerleri arasında pozitif yönde korelasyon saptandı (p<0.05).

statistiksel olarak anlamlı bir farklılık saptandı (p<0.05). Grup İde; IgE, IL-4, IL-10 değerleri ile D vitamini değerleri arasında negatif yönde; IFN- γ değerleri ile D vitamini değerleri arasında pozitif yönde korelasyon saptandı (p<0.05).

Sonuç: Çalışmamızda D vitamininin alerjik rinitli hastalarda Th1/Th2 dengesini etkilediğini ve D vitamini eksikliği ile alerji arasında anlamlı bir ilişki olduğunu saptadık. Bu bulgular alerjik hastalıkların patogenezinde, şiddetinde ve kontrolünde D vitamininin önemli rol oynayabileceğini desteklemektedir. Gelecek çalışmalarda D vitamininin gelişimin hangi basamaklarında, ne kadar dozda ve ne kadar süre verileceği açıklığa kavuşturulmalıdır. Ayrıca D vitamininin alerjik hastalıklar üzerindeki etki mekanizmasını tam olarak ortaya koymak için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Rinit, alerjik, kolekalsiferol, Th1 hücreleri, Th2 hücreleri, interlökin-4, interlökin-10, interferon-gama

Introduction

Allergic rhinitis is the inflammation of the nasal membranes that is characterized by sneezing, nasal congestion, nasal itching, and rhinorrhea in any combination (1). Studies performed in Western Europe have shown that allergic rhinitis has a high prevalence and is frequently undiagnosed (2, 3).

As a steroid hormone, vitamin D₃ is produced in skin and ingested with food and is sequentially metabolized by the liver and kidney to the biologically active form 1α ,25-dihydroxyvitamin D₃ (4). As a modulator of the immune system, it has been demonstrated that vitamin D has complex



This study was presented as a verbal report in 33rd Turkish National Otorhinolaryngology and Head and Neck Surgery Congress, 26-30 October 2011, Antalya, Turkey.

Bu çalışma, 33. Türk Ulusal Kulak Burun Boğaz ve Baş Boyun Cerrahisi Kongresinde sözel bildiri olarak sunulmuştur, 26-30 Ekim 2011, Antalya, Türkiye.

Address for Correspondence/Yazışma Adresi:

Şule Özkar

E-mail: suleozk@msn.com

Received Date/Geliş Tarihi: 19.10.2015

Accepted Date/Kabul Tarihi: 09.01.2016

© Copyright 2015 by Official Journal of the Turkish Society of Otorhinolaryngology and Head and Neck Surgery Available online at www.turkarchotorhinolaryngol.org © Telif Hakkı 2015 Türk Kulak Burun Boğaz ve Baş Boyun Cerrahisi Derneği Makale metnine www.turkarchotorhinolaryngol.org web sayfasından ulaşılabilir. DOI: 10.5152/tao.2015.1187

immunoregulatory effects on both cellular and humoral immune response (5). 1 α ,25-Dihydroxyvitamin D₃ is liposoluble, and it has a nuclear receptor that plays an important role in the regulation of immune response. Most immune cells, including macrophages, T-cells, B-cells, and dendritic cells have a vitamin D receptor (VDR) (4).

The findings that confirm the immunoregulatory effects of vitamin D in allergic diseases are increasing (6, 7). The level of cytokines released by inflammatory cells is reduced by vitamin D; therefore, vitamin D may perform a therapeutic role as an anti-inflammatory agent in allergic disease.

In this study, we aimed to investigate T helper1/T helper2 (Th1/Th2) cell balance by measuring levels of the cytokines interleukin (IL)-4, IL-10, and interferon-gamma (IFN- γ), which play an important role in the immune response of patients with allergic rhinitis, and to determine the correlation between among the Th1/Th2 balance and 1 α ,25-dihydroxyvitamin D₃, the active metabolite of vitamin D.

Methods

We conducted this study at the Ear Nose Throat Clinic at Firat University, School of Medicine, Turkey, with the approval from the Firat University Faculty of Medicine Ethical Committee for Investigations in Humans, between February 2010 and March 2011. All patients and volunteers participating in the study signed an informed consent form. The subjects enrolled in the study were 30 adult patients and 40 healthy volunteers. Furthermore, healthy volunteers including 18 men and 22 women in the control group were aged 18–40 years (mean: 31.2 \pm 7.13 years); 13 men and 17 women in the allergic rhinitis (study) group were similarly aged 18–40 years (mean: 28.7 \pm 6.89 years). Total serum immunoglobulin E (IgE) level examination, a skin prick test, and medical history and examination were performed in all subjects to exclude the presence of allergic rhinitis in the healthy volunteers to confirm the diagnosis in the allergic rhinitis group (8). The control group included 40 healthy volunteers aged 18–40 years, who have no professional and environmental allergen exposure; no allergic rhinitis that is determined by physical examinations, serum total IgE levels, and skin prick test; no allergy symptoms or atopy history, and normal body mass index consistent with their age.

The exclusion criteria for subjects in this study are as follows:

- patients who have used antihistamines during the previous 15 days and steroids during the previous month;
- diseases with the potential to affect the serum 1 α ,25-dihydroxyvitamin D₃ levels (osteoporosis and rickets);
- upper respiratory tract infection, except for allergic rhinitis;
- patients who use drugs with the potential to affect the serum 1 α ,25-dihydroxyvitamin D₃ levels (cholestyramine, phenobarbital, and phenytoin);
- drug-induced rhinitis, nonallergic eosinophilic rhinitis (NARES syndrome), and other acute airway diseases;
- immune system disorders that have the potential to change cytokine levels;
- patients with nasal polyposis or isolated polyps and asthma; asthma diagnosis of the patients is excluded using the diag-

nostic criteria of GINA 2002 guidelines using medical history, physical examination, and pulmonary function tests (9).

Demographical features such as age and sex of all subjects were registered. Blood draws were performed during spring and summer.

The 1 α ,25-dihydroxyvitamin D₃, IL-4, IL-10, IgE and IFN- γ levels were compared between the study and control groups. The degree and direction of reciprocal correlations among IgE, IL-4, IL-10, IFN- γ , and vitamin D levels were calculated in the allergic rhinitis group.

The IL-4, IL-10, and IFN- γ levels were measured using enzyme-linked immunosorbent assay (ELISA), using commercial human IL-4, IL-10 and IFN- γ kits (Boster Immunoleader; Wuhan, China). 1 α ,25-Dihydroxyvitamin D₃ levels were measured using high-pressure liquid chromatography (HPLC) (HPLC equipment by WICOM; Heppenheim, Germany). Skin prick tests were performed in multitest fashion with sterile, disposable plastic applicators. Total serum immunoglobulin levels were analyzed using an N Latex IgE mono kit (Siemens Healthcare Diagnostics Inc.; Newark, NJ, USA) with an automated nephelometer (Dade Behring GmbH; Marburg, Germany) according to the manufacturers' instructions.

Statistical Analysis

SPSS for Windows v11.5 software package (SPSS Inc.; Chicago, IL, USA) is used for the assessment of statistical results. A one-way analysis of variance multiple comparisons test was used for comparing the groups, with *post hoc* analysis using Tukey's honest significant difference (HSD) test. Statistical significance was set at $p \leq 0.05$.

Results

In the control group, mean IgE, IL-4, IL-10, IFN- γ , and vitamin D levels were measured. (IgE: 35.1 \pm 23.1 IU/mL; IFN- γ : 32.1 \pm 20.9 pg/mL; IL-4: 3 \pm 1.9 pg/mL; IL-10: 41.4 \pm 21.8 pg/mL; and 1 α ,25-dihydroxyvitamin D₃: 28 \pm 13.2 μ g/mL). In the study group, IgE, IL-4, IL-10, IFN- γ , and vitamin D mean levels were measured. (IgE: 199.79 \pm 158 IU/mL; IFN- γ : 15.45 \pm 9.5 pg/mL; IL-4: 6.3 \pm 2.9 pg/mL; IL-10: 69 \pm 29.1 pg/mL; and 1 α ,25-dihydroxyvitamin D₃: 10.8 \pm 8.4 μ g/mL).

Table 1. Comparison of IgE, IL-4, IL-10, IFN- γ , and vitamin D levels between the study and control groups

	Study group	Control group	p
IgE	199.81 \pm 158.02	44.82 \pm 38.86	$p < 0.05$
IL-4	6.34 \pm 2.99	3.25 \pm 1.94	$p < 0.05$
IL-10	69.06 \pm 29.11	42.18 \pm 21.18	$p < 0.05$
IFN- γ	15.45 \pm 9.5	30.81 \pm 20.44	$p < 0.05$
Vitamin D	10.89 \pm 8.42	26.51 \pm 13.59	$p < 0.05$

IgE: immunoglobulin E; IL: interleukin; IFN- γ : interferon gamma

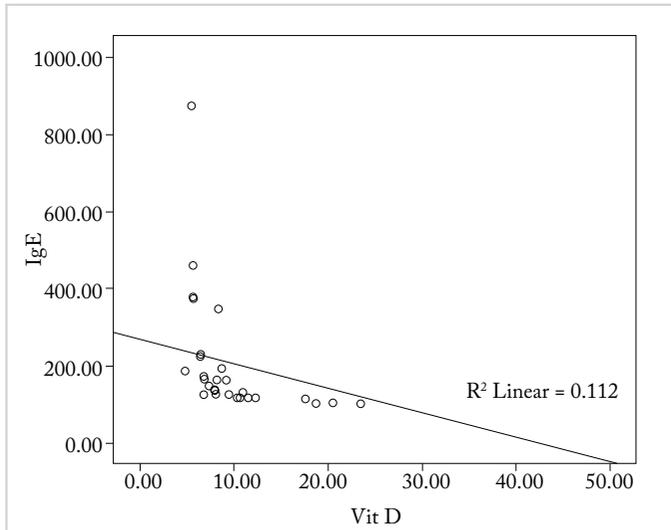


Figure 1. Correlation between vitamin D and IgE in the study group

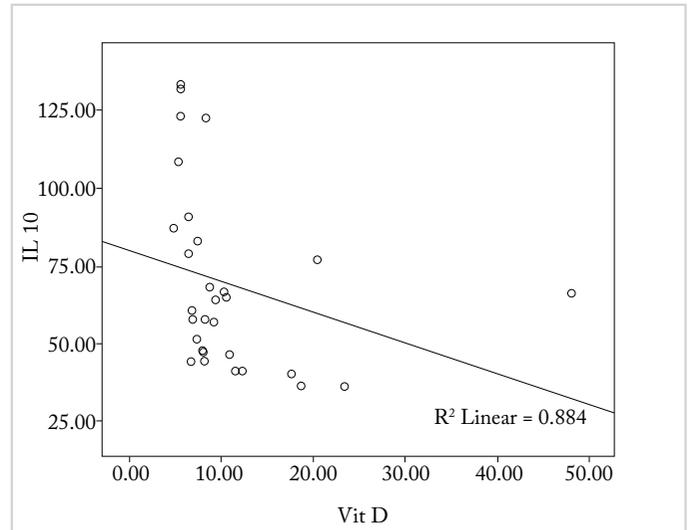


Figure 4. Correlation between vitamin D and IL-10 in the study group

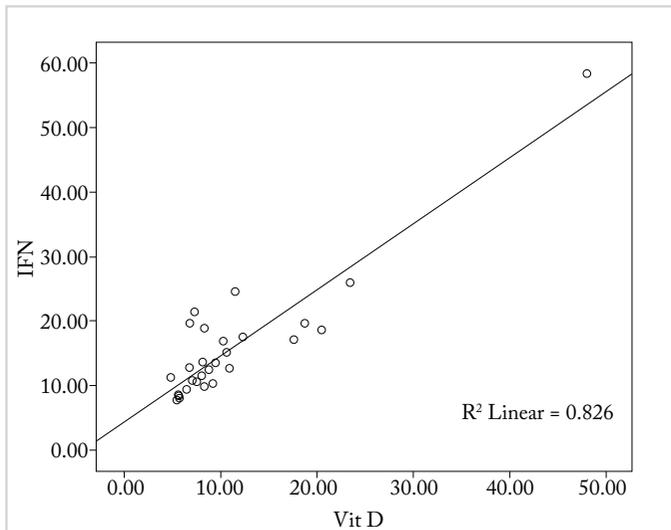


Figure 2. Correlation between vitamin D and IFN-γ in the study group

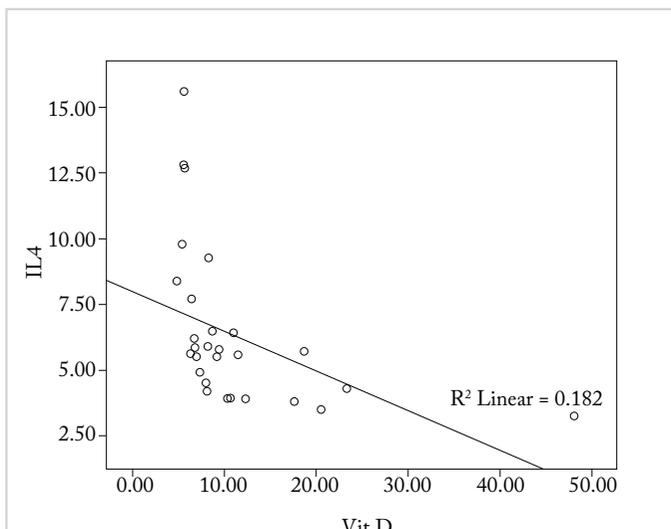


Figure 3. Correlation between vitamin D and IL-4 in the study group

IgE, IL-4, and IL-10 levels in the study group were found to be higher, whereas IFN-γ and 1α,25-dihydroxyvitamin D₃ levels were lower, than those in the control group ($p < 0.05$; Table 1).

With regard to the correlation between the levels of IgE, IL-4, IL-10, and IFN-γ levels and 1α,25-dihydroxyvitamin D₃, it is observed that there is a significant correlation among the increase in IgE, IL-4, and IL-10 levels, and the decrease in IFN-γ and 1α,25-dihydroxyvitamin D₃ levels ($p < 0.05$; Figure 1-4).

Discussion

The significance of vitamin D, 1α,25-dihydroxyvitamin D₃, and VDR has already been mentioned (5). Vitamin D derivatives exert their biological action through their specific nuclear receptor (VDR), present in several immune competent cell types including T and B cells, macrophages, and dendritic cells; they are considered to be significant in asthma and allergic rhinitis (4, 5). The fact that vitamin D appears to reduce inflammatory cytokine release has resulted in speculation regarding a possible therapeutic use in allergic diseases (6, 7).

Different studies indicate a variable effect of 1α,25-dihydroxyvitamin D₃ on cytokine output by Th2 cells (10-18). Various studies show a continuous Th2 response in the presence of 1α,25-dihydroxyvitamin D₃, although some other, and mostly more recent, studies indicate that Th2 response may be inhibited by 1α,25-dihydroxyvitamin D₃ (15, 16). In this study, an inverse correlation of 1α,25-dihydroxyvitamin D₃ levels was found in patients with allergic rhinitis with the levels of IL-4 and IL-10, which are Th2 cytokines ($p < 0.05$).

Studies in animal models have established that vitamin D has a positive effect in autoimmune disease, exerted through a decrease in IFN-γ production (11, 16). Vitamin D reduces IFN-γ synthesis in human cell studies (16, 17).

IFN-γ levels were positively correlated to the 1α,25-dihydroxyvitamin D₃ levels in the allergic rhinitis group ($p < 0.05$). A

statistically significant difference in IFN- γ levels was detected between the study and control groups ($p < 0.05$).

Boonstra et al. (11) reported that vitamin D increased the synthesis of IL-4, IL-5, and IL-10 in a CD4+ T-cell culture. However, Staeva-Vieira and Freedman (15) found that the addition of vitamin D to their CD4+ T-cell culture during the first phase of T-cell differentiation inhibited IL-4 synthesis. Naive T-cells were used in both cases; the cause of this difference in the response to vitamin D is unexplained as yet. It may result from differences in the phases of the CD4+ T-cell differentiation process and their activation status (15). Furthermore, it could be associated with the difference in the vitamin D doses administered in the two studies (17). Studies investigating the circulating Th2 cytokines in peripheral blood following vitamin D or calcitriol administration have shown no evidence of increase in these cytokines (19).

A negative correlation was observed in our study between IL-10 and 1 α ,25-dihydroxyvitamin D₃ levels in patients with allergic rhinitis ($p < 0.05$). A published report has shown that vitamin D, with or without a glucocorticoid, increased IL-10 synthesis by T-cells (20). The mentioned study investigated the action of vitamin D on T_{reg} cells expressing the TLR9 gene. This effect could not be shown in T_{reg} cells without TLR9 gene expression, Th1 cells, or Th2 cells (20).

Domdey et al. (21) showed an elevation of IL-10 levels in atopic patients compared with nonatopic individuals. A statistically significant difference in IL-10 levels was detected among the study and control groups in our study ($p < 0.05$).

In a study, Hyppönen et al. (22) reported a nonlinear association between 1 α ,25-dihydroxyvitamin D₃ and IgE levels. The study indicated that 1 α ,25-dihydroxyvitamin D₃ levels may be low with regard to very low and very high IgE levels. In this study, threshold levels of the effects of 1 α ,25-dihydroxyvitamin D₃ has been mentioned. In our study, we demonstrated that in the study group, there is negative correlation between 1 α ,25-dihydroxyvitamin D₃ and IgE levels ($p < 0.05$).

Several publications document elevated IgE levels in allergic rhinitis (10, 13, 14, 23). This study reported a similar, and statistically significant, difference in the IgE levels between the study and control groups ($p < 0.05$).

Hidaka and Tatsumi (24) reported high IL-4 levels in patients with allergic rhinitis. On comparing IL-4 levels between the allergic rhinitis and control groups in our study, a statistically significant difference was observed ($p < 0.05$).

The studies regarding allergic rhinitis have indicated that Th1/Th2 balance had deteriorated because of Th2 increase (10, 25, 26). In our patients with allergic rhinitis, a strong positive correlation was observed between IgE levels and both IL-4 and IL-10 levels ($p < 0.05$), and a negative correlation was determined between IFN- γ and IgE levels ($p < 0.05$). A moderate negative correlation was determined among IFN- γ levels and both IL-4 and IL-10 levels in the study group ($p < 0.05$). A positive, moderately strong correlation was determined between IL-4 and IL-10 levels

($p < 0.05$). Therefore, in our study, we determined that in the study group, Th1/Th2 balance is impaired with the increase of Th2.

Studies investigating the correlation between 1 α ,25-dihydroxyvitamin D₃ and allergic rhinitis are available in the literature (10, 23-25). Sharief et al. (27) studied the correlation between vitamin D deficiency and allergy in children and teenagers by evaluating the vitamin blood levels and food and peripheral allergens in US. The study demonstrated that there is a correlation between vitamin D deficiency and allergy in these populations; however, this correlation has not been shown in adults. Ehlayel et al. (28) demonstrated that vitamin D deficiency has been observed more often in children who have acute urticaria, asthma, atopic dermatitis, allergic rhinitis, or food allergy. Wjst and Hyppönen (29) demonstrated that allergic rhinitis has been observed more often in a vitamin D deficient population.

In our study, on comparing the groups for their 1 α ,25-dihydroxyvitamin D₃ levels, a statistically significant difference was observed among the allergic rhinitis and control groups ($p < 0.05$).

In our study, 1 α ,25-dihydroxyvitamin D₃ levels were associated with Th1/Th2 balance in allergic rhinitis, and a remarkable interrelation was observed among 1 α ,25-dihydroxyvitamin D₃ deficiency and allergy. These findings show that 1 α ,25-dihydroxyvitamin D₃ may have a remarkable role in the severity and control of allergic disorders. In addition, further investigations are required to confirm how vitamin D should be used in allergic diseases. Moreover, to reveal the exact mechanism of vitamin D on allergic diseases, further studies are required.

Conclusion

1. Levels of 1 α ,25-dihydroxyvitamin D₃, a vitamin D metabolite, in patients with allergic rhinitis are found to be low.
2. When the study and control groups were compared, IgE, IL-4, and IL-10 levels in the study group were higher, whereas IFN- γ and 1 α ,25-dihydroxyvitamin D₃ levels were lower, than those in the control group.
3. With regard to the correlation between IgE, IL-4, IL-10, and IFN- γ levels and 1 α ,25-dihydroxyvitamin D₃ levels, a significant correlation was observed between the increase in IgE, IL-4, and IL-10 levels and the decrease in IFN- γ and 1 α ,25-dihydroxyvitamin D₃ levels.
4. This study is noteworthy for studies that will highlight the correlation among the vitamin D metabolites and allergic diseases.
5. We believe that our study will contribute to other studies with larger series concerning the changes in the allergic rhinitis treatment protocols and the correlation among the vitamin deficiency and the severity of allergic diseases.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Firat University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.K., Ş.Y.; Design - Ş.Ö., N.İ.; Supervision - E.K., T.K.; Resources - Ş.Ö., N.İ., H.G.; Materials - T.K., H.G.; Data Collection and/or Processing - Ş.Ö., Ş.Y.; Analysis and/or Interpretation - E.K., Ş.Y.; Literature Search - N.İ., Ş.Ö.; Writing Manuscript - Ş.Ö., E.K.; Other - T.K., H.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma için etik komite onayı Fırat Üniversitesi Tıp Fakültesi Etik Kurulu'ndan alınmıştır.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - E.K., Ş.Y.; Tasarım - Ş.Ö., N.İ.; Denetleme - E.K., T.K.; Kaynaklar - Ş.Ö., N.İ., H.G.; Gereçler - T.K., H.G.; Veri Toplanması ve/veya İşlenmesi - Ş.Ö., Ş.Y.; Analiz ve/veya Yorum - E.K., Ş.Y.; Literatür Taraması - N.İ., Ş.Ö.; Yazıyı Yazan - Ş.Ö., E.K.; Diğer - T.K., H.G.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

References

- König K, Klemens C, Eder K, San Nicolás M, Becker S, Kramer MF, et al. Cytokine profiles in nasal fluid of patients with seasonal or persistent allergic rhinitis. *Allergy Asthma Clin Immunol* 2015; 1: 26. [\[CrossRef\]](#)
- Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004; 24: 758-64. [\[CrossRef\]](#)
- Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy* 2005; 60: 350-3. [\[CrossRef\]](#)
- Searing DA, Leung DY. Vitamin D in atopic dermatitis, asthma and allergic diseases. *Immunol Allergy Clin North Am* 2010; 30: 397-409. [\[CrossRef\]](#)
- Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D. Modulator of the immune system. *Curr Opin Pharmacol* 2010; 10: 482-96. [\[CrossRef\]](#)
- Sandhu MS, Casale TB. The role of vitamin D in asthma. *Ann Allergy Asthma Immunol* 2010; 105: 191-9. [\[CrossRef\]](#)
- Erkkola M, Kaila M, Nwaru BI, Kronberg-Kippilä C, Ahonen S, Nevalainen J, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clin Exp Allergy* 2009; 39: 875-82. [\[CrossRef\]](#)
- Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008; Suppl 86: 8-160. [\[CrossRef\]](#)
- Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008; 3: 143-78. [\[CrossRef\]](#)
- Ozkara S, Keleş E, İlhan N, Gungor H, Kaygusuz I, Alpay HC. The relationship between Th1/Th2 balance and 1 α ,25-dihydroxyvitamin D₃ in patients with nasal polyposis. *Eur Arch Otorhinolaryngol* 2012; 269: 2519-24. [\[CrossRef\]](#)
- Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HF, O'Garra A. 1 α ,25-dihydroxyvitamin D₃ has a direct effect on naive CD4+ T cells to enhance the development of Th2 cells. *J Immunol* 2001; 167: 4974-80. [\[CrossRef\]](#)
- Goetz DW. Vitamin D treatment of idiopathic itch, rash, and urticaria/angioedema. *Allergy Asthma Proc* 2010; 31: 158-60. [\[CrossRef\]](#)
- Wisniewski JA, Borish L. Novel Cytokines and cytokine-producing T cell in allergic disorders. *Allergy Asthma Proc* 2011; 32:83-94. [\[CrossRef\]](#)
- Broide DH. Allergic rhinitis: Pathophysiology. *Allergy Asthma Proc* 2010; 31: 370-4. [\[CrossRef\]](#)
- Staeva-Vieira TP, Freedman LP. 1,25-dihydroxyvitamin D₃ inhibits IFN- γ and IL-4 levels during in vitro polarization of primary murine CD4+ T cells. *J Immunol* 2002; 168: 1181-9. [\[CrossRef\]](#)
- Mattner F, Smirildo S, Galbiati F. Inhibition of Th1 development and treatment of chronicrelapsing experimental allergic encephalomyelitis by a non-hypercalcemic analogue of 1,25-dihydroxyvitamin D(3). *Eur J Immunol* 2000; 30: 498-508. [\[CrossRef\]](#)
- Mahon BD, Wittke A, Weaver V, Cantorna MT. The targets of vitamin D depend on the differentiation and activation status of CD4 positive T cells. *J Cell Biochem* 2003; 89: 922-32. [\[CrossRef\]](#)
- Sloka S, Silva C, Wang J, Yong VW. Predominance of Th2 polarization by vitamin D through a STAT6-dependent mechanism. *J Neuroinflammation* 2011; 24: 8-56. [\[CrossRef\]](#)
- D'Ambrosio D. Increased IgE but reduced Th2-type inflammation in vitamin D receptor-deficient mice. *J Immunol* 2005; 174: 4451-5. [\[CrossRef\]](#)
- Urry Z, Xystrakis E, Richards DF. Ligation of TLR9 induced on human IL-10-secreting Tregs by 1 α ,25-dihydroxyvitamin D₃ abrogates regulatory function. *J Clin Invest* 2009; 119: 387-98. [\[CrossRef\]](#)
- Domdey A, Liu A, Millner A, Lund K, Jacobi H, Malling HJ, et al. The T cell response to major grass allergens is regulated and includes IL-10 production in atopic but not in non-atopic subjects. *Int Arch Allergy Immunol* 2010; 152: 243-54. [\[CrossRef\]](#)
- Hyppönen E, Berry DJ, Wjst M, Power C. Serum 25-hydroxyvitamin D and IgE - a significant but nonlinear relationship. *Allergy* 2009; 64: 613-20. [\[CrossRef\]](#)
- Sánchez-Segura A, Brieva JA, Rodríguez C. T lymphocytes that infiltrate nasal polyps have a specialized phenotype and produce a mixed TH1/TH2 pattern of cytokines. *J Allergy Clin Immunol* 1998; 102: 953-60. [\[CrossRef\]](#)
- Hidaka Y, Tatsumi K. Secretion of interleukin 4 and immunoglobulin G from peripheral blood mononuclear cells in allergic rhinitis. *J Invest Allergol Clin Immunol* 2007; 17: 413-4.
- Wosinska-Becler K, Plewako H, Håkansson L, Rak S. Cytokine production in peripheral blood cells during and outside the pollen season in birch-allergic patients and non-allergic controls. *Clin Exp Allergy* 2004; 34: 123-30. [\[CrossRef\]](#)
- Benson M, Strannegård IL, Wennergren G, Strannegård O. Low levels of interferon-gamma in nasal fluid accompany raised levels of T-helper 2 cytokines in children with ongoing allergic rhinitis. *Pediatr Allergy Immunol* 2000; 11: 20-8. [\[CrossRef\]](#)
- Sharief S, Jariwala S, Kumar J, Muntner P, Melamed ML. Vitamin D levels and food and environmental allergies in the United States: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol* 2011; 127: 1195-1202. [\[CrossRef\]](#)
- Ehlayel MS, Bener A, Sabbah A. Is high prevalence of vitamin D deficiency evidence for asthma and allergy risks? *Eur Ann Allergy Clin Immunol* 2011; 43: 81-8.
- Wjst M, Hyppönen E. Vitamin D serum levels and allergic rhinitis. *Allergy* 2007; 62: 1085-6. [\[CrossRef\]](#)