ATATÜRK ÜNİVERSİTESİ YAYINLARI
ATATURK UNIVERSITY PUBLICATIONS

Research Article *Araştırma Makalesi* DOI: 10.54614/VetSciPract.2022.985825

Evaluation of Interleukin and Vitamin Levels in Sheep Infested with *Sarcoptes Scabiei*

Sarcoptes Scabiei ile Enfeste Koyunlarda İnterlökin ve Vitamin Düzeylerinin Değerlendirilmesi

Pelin Fatoş POLAT DİNÇER[1]
Ömer Faruk GÖKCECİK[2]
Alper BAŞA[3]

[1]Department of Internal Medicine, Dokuz Eylül University, Faculty of Veterinary Medicine, İzmir, Turkey
[2]Department of Parasitology, Bornova Veterinary Control Institute, İzmir, Turkey
[3]Akçakale Directorate of Provincial Agriculture and Forestry, Şanlıurfa, Turkey

ABSTRACT

This study determined the levels of Vitamin E, 25-hydroxyvitamin D_3 ($25(OH)D_3$), interleukin-2 (IL-2), and interleukin-4 (IL-4) in sheep naturally infected with Sarcoptes scabiei (*S. scabiei*). It also determined the dominant cytokine response and investigated its relationship with $25(OH)D_3$. For this purpose, 20 sheep between the ages of 1-4 years, naturally infected with *S. scabiei*, with crusted wounds were compared with 10 healthy sheep in the same age range. Five ml of blood was collected from each animal and stored at -20 °C until the serum was analyzed. To detect scabies, scrapings were taken and examined under a microscope. Enzyme-linked immunosorbent assay (ELISA) was to determine IL-2 and IL-4 serum levels, high-performance liquid chromatography (HPLC) for Vitamin E analysis, and immunoassay for $25(OH)D_3$ determination. Vitamin E and $25(OH)D_3$ levels were significantly lower in infected sheep compared to the control group ($P < .05$) whereas the IL-4 level of the infected animals was significantly higher ($P < .05$) compared to the control group. There was no significant difference between the groups for IL-2 level ($P > .05$). In conclusion, serum vitamin E and $25(OH)D_3$ levels were lower in crusted scabies in sheep infected with S. scabiei, T lymphocytes had a critical role, and the immune response was in the direction of Th2.

Keywords: Interleukin, vitamin E, 25-hydroxyvitamin D

ÖZ

Çalışmanın amacı S. scabiei ile doğal enfekte koyunlarda vitamin E, 25-hydroxyvitamin D_3 ($25(OH)D_3$), interleukin-2 (IL-2) ve interleukin-4 (IL-4) seviyelerinin tespit edilmesi ayrıca baskın sitokin yanıtının belirlenerek $25(OH)D_3$ ile ilişkisinin araştırılmasıdır. Bu amaçla, 1-4 yaşları arasında *S. scabiei* ile doğal enfekte, kabuklu yaralara sahip 20 ve kontrol grubu olarak aynı yaş aralığında sağlıklı 10 koyun kullanıldı. Her hayvandan 5 ml kan alınıp serumları analiz edilinceye kadar -20 °C'de saklandı. Uyuz akarlarının tespiti için kazıntı alınarak mikroskopta muayene edildi. Serumda IL-2 ve IL-4 tayini enzyme-linked immunosorbent assay (ELİSA), E vitamini analizleri için high-performance liquid chromatography (HPLC) ve 25 $(OH)D_3$ tayini için İmmunoassay kullanıldı. E vitamini ve $25(OH)D_3$ seviyelerinin enfekte koyunlarda kontrol grubuna göre istatistiksel olarak azaldığı ($P < ,05$) görüldü. Enfekte hayvanların IL-4 seviyesi kontrol grubuna göre istatistiksel olarak artış ($P < ,05$) gösterirken, IL-2 seviyesinde gruplar arasında istatistiksel fark tespit edilemedi ($P > ,05$). Sonuç olarak, S. scabiei ile enfekte koyunlarda meydana gelen kabuklu uyuzlarda serum E vitamini ve $25(OH)D_3$ düzeylerinin azaldığı, T lenfositlerin kritik rolünün olduğu ve immun yanıtın Th2 yönünde olduğu görülmüştür.

Anahtar Kelimeler: İnterlökin, E Vitamini, 25-hidroksivitamin D

Received/Geliş Tarihi: 22.08.2021
Accepted/Kabul Tarihi: 04.01.2022

Corresponding Author/Sorumlu Yazar:
Pelin Fatoş POLAT DİNÇER
E-mail: pelinfatos.polat@deu.edu.tr

Cite this article: Polat Dinçer PF, Gökcecik ÖF, Başa A. Evaluation of interleukin and vitamin levels in sheep infested with *sarcoptes scabiei*. *Vet Sci Pract. 2022; 17*(1), 11-15.

Atıf: Polat Dinçer PF, Gökcecik ÖF, Başa A. Sarcoptes Scabiei ile Enfeste Koyunlarda İnterlökin ve Vitamin Düzeylerinin Değerlendirilmesi. *Vet Sci Pract. 2022;17*(1), 11-15.

INTRODUCTION

Sarcoptic mange is a parasitic skin disease caused by the *Sarcoptes scabiei (S. scabiei)* mite. In sheep, lesions characterized by the formation of crusts up to 1 cm thick are mainly located in the head region.[1] The main clinical symptom is rubbing and itching as well as dry skin, dandruff, and cracks. Epidemics, which appear every season when sheep numbers are high, cause significant financial losses due to low feed efficiency and birth weight, poor fleece quality, and deaths in advanced cases.[2]

When the mite infects the host, a process begins between the mite and the skin, which determines the course of infestation and the severity of clinical symptoms. When scabies mites enter the skin, they secrete substances that induce inflammatory and immune responses, as well as substances that allow the mite to circumvent the host's protective mechanisms and suppress certain aspects of the host. As the infestation progresses and the mites multiply, the host's immune system is activated. Located under the epidermis, the mites release antigenic and pharmacologically active substances (saliva, molting enzymes and hormones, feces and nitrogen) that are dispersed into the fluid between the epidermal and dermal cells. These substances induce responses from keratinocytes, fibroblasts, macrophages, mast cells, lymphocytes, langerhans cells, dendritic cells, and microvascular-type endothelial cells.[3]

Histopathological examination of skin biopsies taken from scabies lesions show inflammatory cell infiltrates containing eosinophils, lymphocytes, and macrophages around the cavities caused by scabies.[4] The predominant lympho-

cytes in the infiltrate are T lymphocytes, which play a central role in the activation and regulation of immune responses by recognizing antigens and inducing cytokine production. Keratinocytes produce proinflammatory cytokines while immunomodulatory cytokines are responsible for systemic effects.[5,6] Eosinophils are multifunctional leukocytes that play a role in the pathogenesis of numerous inflammatory processes, including parasitic infestations and allergic disorders.[7] They secrete a number of cytokines (IL-2, IL-4, IL-6, IL-10, IL-12) that can promote T cell proliferation, activation, and Th1/Th2 polarization.[8,9]

Studies have reported a link between the presence of Vitamin D receptors (VDR) in various immune cells, such as monocytes, macrophages, and activated T and B cells, and the immune system.[10] Vitamin D inhibits T cell proliferation and the production of cytokines, such as interleukin-2 (IL-2), interleukin-12 (IL-12), and Interferon Gamma (IFN-y) in vitro. Stimulation of Th2 cells to produce anti-inflammatory cytokines (TGF-beta-1, IL-1, IL-4) produces anti-inflammatory effects both in vivo and in vitro.[11,12]

Free radicals are reactive molecules produced in different metabolic processes in the body. Antioxidant vitamins like Vitamin E prevent free radical formation.[13] In addition, Vitamin E is very important for cellular and humoral immunity because it modulates Th1 and Th2 responses with its effects on polarization from CD4+ T cells to Th1 or Th2 cells, protection against intracellular and extracellular pathogens, and the development of different types of chronic diseases (inflammatory and allergic diseases).[14]

This study aimed to measure levels of Vitamin E, 25-hydroxyvitamin D_3 (25(OH)D_3), IL-2, and IL-4 in sheep naturally infected with *S. Scabiei*, determine the dominant cytokine response. The results can contribute to pathobiological knowledge of the disease and treatment and prophylaxis of sheep infected with *S. scabiei*.

MATERIAL AND METHODS

Animals and Study Design

Twenty sheep between the ages of 1-4 years, naturally infected with *S. scabiei* and with crusted wounds were compared to 10 healthy sheep in the same age range. None of the animals had been treated with corticosteroids or vitamins. Five ml of blood was collected from the V. jugularis of the sheep in yellow-capped (BD Vacutainer® SST™II Advance) tubes. After the blood samples were centrifuged (Nuve, NF 800R, Turkey) at 3000rpm/10min serum samples were stored at -20 °C until analysis. Before starting the study, ethical approval was obtained from Dokuz Eylül University Animal Experiments Local Ethics Committee, dated 14.07.2021, decision number 42/2021.

Skin Scraping Examination

To detect scabies mites, skin scraping samples were taken from at least two different areas and a 1 cm^2 area adjacent to healthy tissue.[15] The scraping samples were taken in 10% KOH and kept at 37°C for 1 day. After centrifugation (Thermo Fisher Scientific, Germany) at 3000 rpm / 3 min, the precipitate was examined under a microscope (Olympus, SZX7, Japan) at x4 and x10 magnification.[16]

Evaluation of Immune and Vitamin Profile

Sheep IL-2 ELISA kit (E0029Sh, Bioassay Technology Laboratory, China) and sheep IL-4 ELISA kit (E0079Sh, Bioassay Technology Laboratory, China) were used to measure IL-2 and IL-4 serum levels. Enzyme-linked immunosorbent assay (ELISA) analyses were performed in accordance with the kit supplier's instructions. For the detection of 25(OH)D_3, a serum sample chromatography (HPLC) instrument was used (Shimadzu OGU-20A, Japan) while a high performance liquid was used for Vitamin E analysis from the Immunoassay instrument (Siemens AdviaCentaur XP, Germany).

Statistical Analysis

Statistical analyzes were performed using IBM Statistical Package for the Social Sciences (IBM SPSS Armonk, NY, USA) version 22. Both visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov) were used to determine whether the variables were normally distributed. Student's t-test was used for the normally distributed vitamin and cytokine parameters. A p value less than .05 was considered a statistically significant result.[17]

RESULTS

Under microscopic examination of the scraping samples, the active ingredient *Sarcoptes scabiei var. ovis* was detected (Figure 1). Hypersensitivity, alopecia, pruritis, crust formation, and deep skin cracks were observed macroscopically, especially in the face and ears of the all infected sheep. Vitamin E levels were significantly lower ($P < .05$) in the infected sheep (0.51 ± 0.15 mg/L) compared to the control group (1.45 ± 0.30 mg/L) (Figure 2). Similarly, 25(OH)D_3 levels were significantly lower ($P < .05$) in the infected sheep (26.16 ± 1.04 ng/mL) compared to the control group (66.29 ± 4.45 ng/mL) (Figure 3). Conversely, IL-4 interleukin levels were significantly higher ($P < .05$) in the infected animals (35.26 ± 5.08 ng/L) compared to the control group (22.76 ± 2.86 ng/L). For IL-2, however, there was no significant difference ($P > .05$) in levels in the infected sheep (14.41 ± 2.28 ng/L) and control group (12.50 ± 2.31 ng/L) (Figure 4).

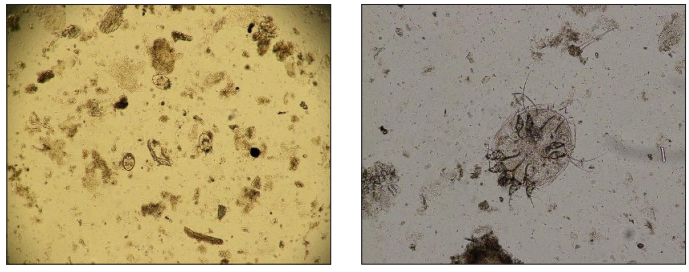

Figure 1. Microscope image of *S. scabiei* (magnification 4× and 10×)

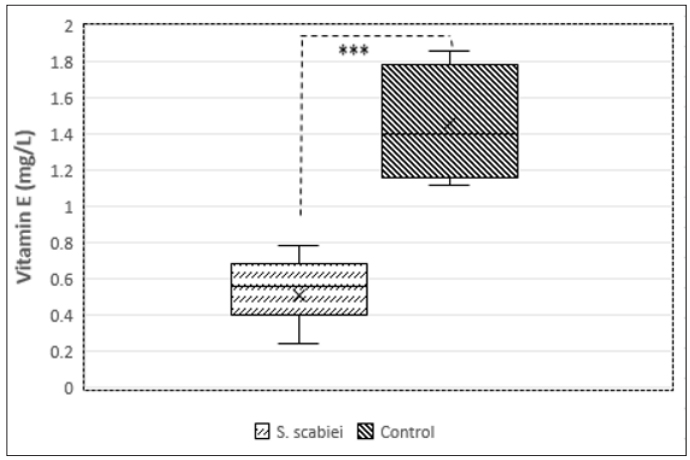

Figure 2. Serum vitamin E level in sheep infected with *S. scabiei*. Bars represent mean ± SE, *** < .05.

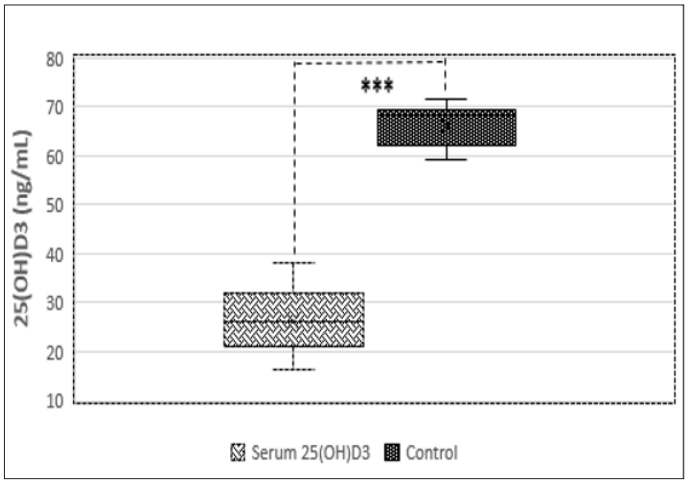

Figure 3. Serum 25 (OH)D3 level in sheep infected with *S. scrabiei*. Bars represent mean ± SE, *** < .05.

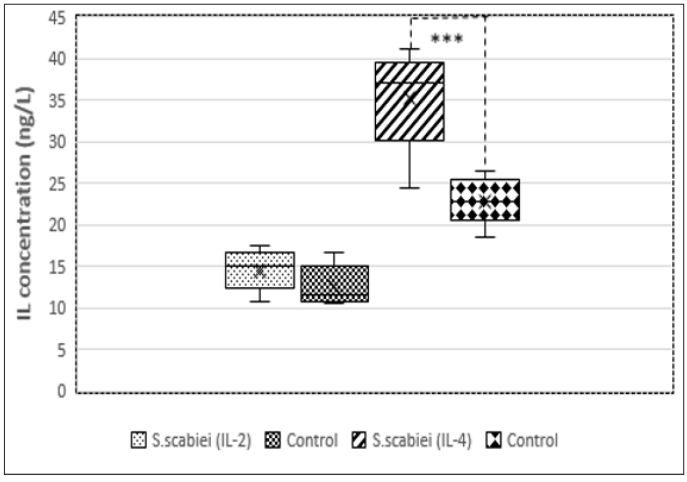

Figure 4. Serum interleukin levels in sheep infected with *S. scabiei*. Bars represent mean ± SE, *** < .05.

DISCUSSION

Parasitic skin disease caused by the *S. scabiei* mite causes severe epidemics that result in economic losses due to low milk production and wool quality, growth retardation in newborn lambs, and death in advanced cases.[2] In addition, animal welfare is reduced by severe itching and rubbing symptoms.

Cytokine secretion from T lymphocytes plays an important role in the immune response to parasitic skin infestations. Evaluation of cytokine profiles in sheep naturally infected with *S. scabiei* is important for understanding the pathobiology of scabies. Therefore, this study investigated cytokine profiles and Vitamin E and 25(OH)D_3 levels, which are closely related to immune system function, in sarcoptic sheep.

In line with previous studies, Vitamin E levels were significantly lower in sheep with S. scrabiei compared to the control group. Bickhardt et al.[18] examined Vitamin E levels in 125 sheep and 32 goats between 1991 and 1998 with general motor disorders or high plasma creatine kinase. They reported deficient Vitamin E levels below 1.0 mg/l. Based on this data, sheep with S. scrabiei may suffer severe Vitamin E deficiency. Similarly, Dimri et al.[13] reported severe Vitamin E deficiency and high mortality in a herd of cows infested with sarcoptic mange. Regarding immunity, dietary Vitamin E supplements increase cell-mediated and humoral immune responses in various animal species, and increased lymphocyte proliferation, immunoglobulin levels, antibody responses, natural killer (NK) cell activity, and IL-2 production.[19] Li-Weber et al.[20] treated allergic donors with Vitamin E and reported a decrease in IL-4 production. Malmberg et al.[21] reported that the frequency of CD4+ T cells producing IL-2 and the production of IFN-γ increased in colorectal cancer patients after two weeks of 750 mg Vitamin E supplementation. Han et al.[22] reported increased Th1 response and decreased viral titer in old mice lungs following 500 ppm Vitamin E supplementation eight weeks before infection with influenza virus.

In our study, 25(OH)D_3 levels were significantly lower in sheep naturally infected with S. scrabiei compared to the control group. Similarly, Ural et al.[23] reported significantly lower 25(OH)D_3 levels compared to the control group of 28 sheep infected with *S. scabiei* Başbuğ et al.[24] found 25(OH)D_3 levels were lower in 14 sheep with caseous lymphadenitis compared to the control group.

The functional integration of the immune system is mainly accomplished by cell-to-cell communication based on small molecule cytokines.[25] Th1 lymphocytes are characterized by the production of IFN-γ and IL-2 cytokines while Th2 lymphocytes are characterized by the production of IL-4 and IL-5 related to the humoral immune response.[26] Th1 and Th2 cells are seen in almost all known immune response patterns. Th1 cells are hypothesized to lead the attack against intracellular pathogens, such as viruses, increase the classical delayed-type hypersensitivity skin response to viral and bacterial antigens, and fight cancer cells. Th2 cells are believed to provide protection against extracellular pathogens, such as multicellular parasites.[25]

Scabies infestation impairs the Th1/Th2 immune response.[27] In our study, IL-4 levels were significantly lower in sheep with crusted wounds infected with *S. scabiei* compared to the control group. The dominant cytokine response in this disease is in the direction of Th2 while various studies have reported overproduction of Th2 specific cytokines and increased allergic immune response to sarcoptes.[5,26,28-30] Sarre et al.[31] performed transcriptional analysis of skin biopsies from cattle with psoroptic crustacean scabies, and found similarly increased expression of IL-4, IL-5, and IL-13. Singh et al.[26] reported that IL-4 and IL-5 production increases in dogs naturally infected with *S. scabiei* var. Canis, which plays a role in the immunopathogenesis of dogs. Bayraktar et al.[32] found a 65.7% increase in IL-4 and a 46.8% increase in IL-2 levels in people infected with cystic echinococcosis.

In contrast to our findings, Al-Musawi et al.[9] investigated the immune response in 60 cases of scabies, of which 30 were early and 30 late. They reported that the host immune response was similar to the Th2 allergic response in patients with early scabies, while it was in the form of a Th1 cell-mediated immune response in late scabies patients. The increase in IL-4 levels in sheep infected with *S. scabiei* helps recruit B cells, mast cells, and eosinophils that can produce IgE antibodies, which play an important role in inducing allergic symptomatology.[33] In particular, eosinophils are produced in large amounts in inflammatory areas under allergic conditions and helminth infestations.[34] Eosinophils also express Th2-specific cytokines.[35] Van den Broek et al.[36] determined that the dominant immune inflammatory infiltrate in sheep infected with Psoroptes ovis was eosinophil. This explains the Th2-directed immune response in sheep infected with *S. scabiei*.

The active form of Vitamin D, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), is an endocrine regulator of calcium homeostasis. Recent studies have shown that local production of $1,25(OH)_2D_3$ by immune cells has autocrine and paracrine immunomodulatory effects. T cells cause an increase in IL-4 and IL-5 but a decrease in IL-2 and IFNy, which reduces the Th1/Th2 response.[37] Based on the ability of $1,25(OH)_2D_3$ to suppress the development of various autoimmune diseases and prolong allograft survival, it was named $1,25(OH)_2D_3$ immunosuppressive hormone.[38] Smolders et al.[39] investigated the effect of high Vitamin D levels in multiple sclerosis (MS) patients and found that the dominant response in Th1/Th2 balance was Th2 while Vitamin D could provide important support for MS patients. However, Vitamin D has no effect on the susceptibility of mice to Herpes simplex virus or Candida albicans infections.[40] Meckel et al.[41] reported a relationship between inflammation and low serum $25(OH)D_3$.

Little is known about the role of Vitamin D in regulating immune responses to infectious diseases. Other than the ability of this nutrient or hormone to suppress autoimmune diseases and prolong transplantation, most of what is known is open to further research.[38] Jiao et al.[42] found a decrease in IFN-γ and Th1/Th2 levels and an increase in IL-4 levels in rats with Vitamin D deficiency whereas the opposite was true for rats that received Vitamin D supplementation during pregnancy.[41]

In conclusion, regarding sheep with crusted scabies infected with *S. Scabiei*, this study showed that serum Vitamin E and $25(OH)D_3$ levels decreased, T lymphocytes played a critical role, and a Th2 immune response occurred.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dokuz Eylül University (Date: July 14, 2021, Decision Number: 42/2021).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.F.P.D.; Design – P.F.P.D.; Supervision – P.F.P.D.; Resources – P.F.P.D.; Data Collection and/or Processing – A.B., Ö.F.G.; Analysis and/or Interpretation – P.F.P.D.; Literature Search – P.F.P.D.; Writing Manuscript– P.F.P.D.; Critical Review – P.F.P.D., Ö.F.G.

Declaration of Interests: The authors have no conflicts of interest to declare.

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

Etik Komite Onayı: Bu çalışma için etik komite onayı Dokuz Eylül Üniversitesi'nden (Tarih: 14 Temmuz 2021, Karar No: 42/2021) alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir – P.F.P.D.; Tasarım – P.F.P.D.; Denetleme – P.F.P.D.; Kaynaklar – P.F.P.D.; Veri Toplanması ve/veya İşlemesi – A.B., Ö.F.G.; Analiz ve/veya Yorum – P.F.P.D.; Literatür Taraması – P.F.P.D.; Yazıyı Yazan – P.F.P.D.; Eleştirel İnceleme – P.F.P.D., Ö.F.G.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

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

REFERENCES

1. Cordero del Campillo M, Rojo-Vazquez FA. *Parasitologia Veterinaria*. 1st edn., McGraw-Hill Interamericana, Spain, 1999.
2. Doukas D, Lıakou Z, Tontis D. Sarcoptes scabiei dermatitis in adult sheep: an immunohistochemical study of 34 chronic cases with extensive lesions. *J Hell Vet Medical Soc*. 2021;72(1):2755-2764. [Crossref]
3. Arlian LG, Morgan MS. A review of Sarcoptes scabiei: past, present and future. *Parasites & Vectors*. 2017;10(1):1-22. [Crossref]
4. Walton SF, Currie BJ. Problems in diagnosing scabies, a global disease in human and animal populations. *Clin Microbiol Rev*. 2007;20(2):268-279. [Crossref]
5. Walton SF, Pizzutto S, Slender A, et al. Increased allergic immune response to arcoptes scabiei antigens in crusted versus ordinary scabies. *Clin Vaccine Immunol*. 2010;17(9):1428-1438. [Crossref]
6. Jiang Y, Tsoi LC, Billi AC, et al. Cytokinocytes: the diverse contribution of keratinocytes to immune responses in skin. *JCI Insight*. 2020;5(20):1-15. [Crossref]
7. Akdis CA, Arkwright PD, Brüggen MC, et al. Type 2 immunity in the skin and lungs. *Allergy*. 2020;75(7):1582-1605. [Crossref]
8. Stephen B, Hajjar J. Overview of basic immunology and clinical application. *Adv Exp Med Biol*. 2020;1244:1-36. [Crossref]
9. Al-Musawi MM, Hasan HR, Maluki AH. Relationship between TH1, TH2 immune responses and serum SOD activity in scabies. *J Adv Biomed Pathobiol Res*. 2014;4(1):1-15.
10. Martens PJ, Gysemans C, Verstuyf A, Mathieu C. Vitamin D's effect on immune function. *Nutrients*. 2020;12(5):1248. [Crossref]
11. Bishop EL, Ismailova A, Dimeloe S, Hewison M, White JH. Vitamin D and immune regulation: antibacterial, antiviral, anti-inflammatory. *JBMR Plus*. 2021;5(1):e10405. [Crossref]
12. Karagöz Güral N. *Köpeklerde Bazı Paraziter Dermatozlarda Serum 25 Hidroksi Vitamin D3 Düzeyinin Belirlenmesi*. Adnan Menderes Üniversitesi, Sağlık Bilimleri Enstitüsü, Türkiye, 2017.
13. Dimri U, Sharma MC, Yamdagni A, Ranjan R, Zama MMS. Psoroptic mange infestation increases oxidative stress and decreases antioxidant status in sheep. *Vet Parasitol*. 2010;168(3-4):318-322. [Crossref]
14. Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system-working in harmony to reduce the risk of infection. *Nutrients*. 2020;12(1):236. [Crossref]
15. Fthenakis GC, Papadopoulos E, Himonas C, Leontides L, Kritas S, Papatsas J. Efficacy of moxidectin against sarcoptic mange and effects on milk yield of ewes and growth of lambs. *Vet Parasitol*. 2000;87(2-3):207-216. [Crossref]
16. William MS, Margo JP, Alan Kocan A. *Parasitic diseases of wild mammals*. 1st edn., 115, Iowa state university press, Ames, 2001.
17. Hayran M, Hayran M. *Sağlık Araştırmaları İçin Temel İstatistik*. 2st edn., Azim Matbaacılık, Ankara, Türkiye, 2018.
18. Bickhardt K, Ganter M, Sallmann P, Fuhrmann H. Investigations on manifestations of vitamin E and selenium deficiency in sheep and goats. *Dtsch Tierarztl Wschr*. 1999;106(6):242-247.
19. Lewis ED, Meydani, SN, Wu D. Regulatory role of vitamin E in the immune system and inflammation. *IUBMB Life*. 2019;71(4):487-494. [Crossref]
20. Li-Weber M, Giaisi M, Treiber MK, Krammer PH. Vitamin E inhibits IL-4 gene expression in peripheralv blood T cells. *Eur J Immunol*. 2002;32(9):2401-2408. [Crossref]
21. Malmberg KJ, Lenkei R, Petersson M, et al. Short-term dietary supplementation of high doses of vitamin E increases T helper 1 cytokine production in patients with advanced colorectal cancer. *Clin Cancer Res*. 2002;8(6):1772-1778.
22. Han SN, Wu D, Ha WK, et al. Vitamin E supplementation increases T helper 1 cytokine production in old mice infected with influenza virus. *Immunology*. 2000;100(4):487-493. [Crossref]
23. Ural K, Tunca R, Ural DA, et al. Interpretation of serum 25-hydroxy vitamin D3 concentartions in sheep with naturally occurring sarcoptic mange. *J Adv VetBio Sci Tech*. 2018;3(1):35-40. [Crossref]
24. Başbuğ O, Tuzcu N, Ercan N, Aydoğdu U, Oğrak YZ. Serum vitamin D levels in sheep with Caseous Lymphadenitis. *FÜ Sağ Bil Vet Derg*. 2014;28(2):77-80.
25. Hammouda MB, Ford AE, Liu Y, Zhang JY. The JNK signaling pathway in inflammatory skin disorders and cancer. *Cells*. 2020;9(4):857. [Crossref]

26. Singh SK, Dimri U, Sharma B, Saxena M, Kumari P. Assessment of the cytokine profile in peripheral blood mononuclear cells of naturally Sarcoptes scabiei var. canis infested dogs. *Vet Parasitol*. 2014;206(3-4):253-257. [Crossref]
27. Lalli PN, Morgan MS, Arlian LG. Skewed Th1/Th2 immune response to Sarcoptes scabiei. *J Parasitol*. 2004;90(4):711-714. [Crossref]
28. Mounsey KE, McCarthy JS, Walton SF. Scratching the itch: new tools to advance understanding of scabies. *Trends Parasitol*. 2013;29(1):35-42. [Crossref]
29. Walton SF, Beroukas D, Roberts-Thomson P, Currie BJ. New insights into disease pathogenesis in crusted (Norwegian) scabies: the skin immune response in crusted scabies. *Br J Dermatol*. 2008;158(6):1247-1255. [Crossref]
30. Roberts LJ, Huffam SE, Walton SF, Currie BJ. Crusted scabies: clinical and immunological findings in seventy-eight patients and a review of the literature. *J Infect*. 2005; 50(5):375-381. [Crossref]
31. Sarre C, Gonzalez-Hernandez A, Van Coppernolle S, et al. Comparative immune responses against Psoroptes ovis in two cattle breeds with different susceptibility to mange. *Vet Res*. 2015;46(1):1-10. [Crossref]
32. Bayraktar MR, Mehmet N, Durmaz R. Th1 and Th2 inducing cytokines in Cystic echinococcosis. *Turkiye Parazitol Derg*. 2005;29(3):167-170.
33. Maggi E. The TH1/TH2 paradigm in allergy. *Immunotechnology*. 1998;3(4):233-244. [Crossref]
34. Stone KD, Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol*. 2006;125(2):73-80. [Crossref]
35. Bhat SA, Mounsey KE, Liu X, Walton SF. Host immune responses to the itch mite, Sarcoptes scabiei, in humans. *Parasites & Vectors*. 2017;10(1):1-12. [Crossref]
36. Van den Broek AH, Huntley JF, MacHell J, et al. Cutaneous and systemic responses during primary and challenge infestations of sheep with the sheep scab mite, Psoroptes ovis. *Parasite Immunol*. 2000; 22(8):407-414. [Crossref]
37. Guillot X, Semerano L, Saidenberg-Kermanac'h N, Falgarone G, Boissier MC. Vitamin D and inflammation. *Jt Bone Spine*. 2010;77(6):552-557. [Crossref]
38. Cantorna MT, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1, 25-dihydroxyvitamin D3, and the immune system. *Am J Clin Nutr*. 2004; 80(6):1717-1720. [Crossref]
39. Smolders J, Thewissen M, Peelen E, et al. Vitamin D status is positively correlated with regulatory T cell function in patients with multiple sclerosis. *PloS One*. 2009;4(8):e6635. [Crossref]
40. Cantorna MT, Hullett DA, Redaelli C, Brandt CR, Humpal-Winter J, Sollinger HW, Hector D. 1, 25-Dihydroxyvitamin D3 prolongs graft survival without compromising host resistance to infection or bone mineral density. *Transplantation*. 1998;66(7):828-831. [Crossref]
41. Meckel K, Li YC, Lim J, Kocherginsky M, Weber C, Almoghrabi A, Cohen RD. Serum 25- hydroxyvitamin D concentration is inversely associated with mucosal inflammation in patients with ulcerative colitis. *Am J Clin Nutr*. 2016;104(1):113-120. [Crossref]
42. Jiao X, Wang L, Wei Z, Liu B, Liu X, Yu X. Vitamin D deficiency during pregnancy affects the function of Th1/Th2 cells and methylation of IFN-γ gene in offspring rats. *Immunol Lett*. 2019;212:98-105. [Crossref]