http://www.pjbs.org

PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

OPEN ACCESS

Pakistan Journal of Biological Sciences

ISSN 1028-8880
DOI: 10.3923/pjbs.2024.27.34

CrossMark

Research Article

Correlation Between a Deficiency of D3 Levels and the Development of Allergic Rhinitis

[1]Rojan Ghanim Mohammad Al-Allaff and [2]Tuka Moayed Bakr Al-Sawaf

[1]Department of Biology, College of Sciences, University of Mosul, Mosul, Iraq
[2]Department of Anatomy, College of Medicine, Ninevah University, Mosul, Iraq

Abstract

Background and Objective: Allergic rhinitis (AR) is a common disorder characterized by sneezing, runny nose, nasal congestion and lacrimation, which negatively affects the quality of life to a large extent. The study aimed to find a link between the effect of vitamin D3 levels on Immunoglobulin (IgE) levels in patients with allergic AR. **Materials and Methods:** This study included 30 patients with AR, with ages ranging from 18 to 35, of both sexes. For vitamin D levels, $\geq$30 ng/mL is considered sufficient and $\leq$20 ng/mL is a deficiency. The second group includes 30 people with adequate levels of vitamin D3 as a control group. All results were analyzed statistically by ANOVA, in addition to using the regression coefficient test to test the extent of the effect of D3 on the development of allergic rhinitis at a significant level of $p\leq 0.05$ using the SPSS program 24. **Results:** The results showed a significant decrease in the levels of vitamin D3 in the serum of the AR patients compared with the control group and a substantial increase in the levels of IgE in the serum of the AR patients compared with the control group at a significant level of $p\leq 0.05$. Additionally, the results showed in the regression coefficient an inverse and significant effect of vitamin D3 concentration on serum IgE levels, which is significant in terms of the p-value, which appeared equal to 0.010. By observing the value of the R^2 coefficient of determination, it is clear that a change in the concentration of vitamin D3 causes 58% of the changes in IgE levels. **Conclusion:** Through linear regression correlation, an inverse linear relationship emerged linking low vitamin D3 levels to increased IgE levels with an effect rate of 58%.

Key words: Allergic rhinitis, D3, IgE, regression coefficient, vitamin, WBCs

Citation: Al-Allaff, R.G.M. and T.M.B. Al-Sawaf, 2024. Correlation between a deficiency of D3 levels and the development of allergic rhinitis. Pak. J. Biol. Sci., 27: 27-34.

Corresponding Author: Rojan Ghanim Mohammad Al-Allaff, Department of Biology, College of Sciences, University of Mosul, Mosul, Iraq

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The AR is a seasonal, non-contagious rhinitis and it is widespread all over the world. The symptoms appear in the form of sneezing and coughing, similar to the symptoms of influenza. The AR is an immunological phenomenon that begins when the cause of the allergic condition enters the nasal mucosa, leading to the emergence of a group of inflammatory responses that end with the appearance of IgE, which in turn binds to the antigen and settles on its receptors on the surface of microglial cells, which leads to the secretion of histamine to the bloodstream in large quantities. Due to the lack of a definite and unambiguous aetiology, there is no considerable control over the disease[1].

The AR aetiology is still a hot topic in medical studies. Vitamin D3 insufficiency has been studied and reported as a possible cause of allergic diseases such as food allergies[2], asthma[3] and eczema[4]. Some researchers have connected vitamin D3 insufficiency to the aetiology or progression of AR. Vitamin D3 affects the activity of specialized and non-specialized immunity, as it regulates the effectiveness of B cells, T cells, macrophages and mononuclear cells. It also regulates the stimulation of immune responses by controlling the efficacy of various cytokines and the production of IgE, which mediate allergic disorders. Because vitamin D3 also plays a function in regulating the immune response, researchers focused on a follow-up study of the effect of vitamin D3 deficiency on the development of allergic conditions and it was taken into consideration that nutritional supplements have a therapeutic and preventive role in people with AR[5,6].

The term 'vitamin D' refers to the presence of two kinds of vitamin, D2 and D3, in the body. Humans obtain vitamin D through diet, nutritional supplements and endogenous synthesis through the skin. Vitamin D is abundant in fish and meals supplemented with vitamin D2 or D3, particularly dairy products and wheat cereals eaten for breakfast[7].

The first step in endogenous vitamin D production involves the absorption of Ultraviolet B (UVB) radiation by 7-dehydrocholesterol under the skin, producing previtamin D3, which is quickly converted to vitamin D3[8]. This process depends mainly on the ability of the UVB photon to penetrate the body through the skin and it has been observed that the entry of these photons is significantly reduced in the presence of dark pigmentation on the skin surface[9].

Vitamin D has lately garnered greater attention due to its effects on numerous chronic diseases, including cancer, autoimmune disorders, diabetes and nervous system problems. One study proved that vitamin D directly or indirectly affects the activity of more than 900 genes in the human body. It was noted that its importance increased through its control of the responses of immune system cells. The discovery of vitamin D3 receptors (VDR) on the surfaces of many cells of the immune system also led to an understanding of how it works and the sensitive role it plays within the body[10].

The present research project sought to investigate the impact of low vitamin D3 levels on the development of AR by following some immune changes in people with low vitamin D3 levels and the extent of the effect of this decrease on the total absolute numbers of neutrophils, lymphocytes and monocytes, in addition to the levels of IgE. In addition to estimating the extent of development of AR with variation in vitamin D3 levels using the regression coefficient test.

MATERIALS AND METHODS

Study area: The study was conducted in the Advanced Immunology Laboratory of the College of Science, Department of Biology (University of Mosul) for the period from 01-06-2023 until 01-12-2023.

Study groups: This study included 30 patients of both sexes with AR, aged 18-35 years. The AR was diagnosed based on patient and family history, the clinical signs associated with the allergic condition and the physical findings that coincide with it. The most important of these symptoms are runny nose, paleness of the face, inflammation of the inner mucous layer of the nose, red eyes, nasal congestion, watery or itchy nose and frequent sneezing attacks[11,12]. For vitamin D levels, $\geq$30 ng/mL is considered adequate and $\leq$20 ng/mL is considered a vitamin D deficiency[13]. The second group includes 30 people with sufficient levels of vitamin D3 and do not show any symptoms of AR as a control group.

Collection of blood and serum: Five millilitres of venous blood were taken from each participant. One milliliter of blood was deposited in an ethylenediaminetetraacetic acid tube to complete the blood count. The remaining blood samples were centrifuged at 3000 rpm/5 min after clotting in a gel tube for 5 min at 37°C. Separated serum was collected in Eppendorf tubes and kept at 20°C for vitamin D3 testing and serum IgE detection.

Estimation of vitamin D3 levels: The test was performed using Cobas e114 equipment of German origin. A VIDAS® device was used to estimate total vitamin D3.

Procedure: For each sample, control, or calibrator to be examined, one VITD strip and another solid phase receptacle (SPR)® VITD strip from the kit is used. The VITD icon on the gadget indicates the test. The S1 also identifies the calibrator and C1 must be used to identify the control under test after it has been recognized. A vortex mixer (CYAN/Belgium) combined the calibrator, screen and samples (for serum or plasma isolated from the pellet). The SPR and VITD strips were placed into the device after calibrating the calibration section, control and test sample to 100 µL. The scan has begun as instructed in the user handbook. The tool performed all the scan procedures and executed all scanning stages automatically. The flasks were resealed and returned to 2-8°C after absorption. The duration of the examination was 40 min.

Complete blood count: This was accomplished using an automated Nihon Kohden of Japanese origin, which read 18 hematological parameters.

IgE estimation: Use a VIDAS device from France origin to estimate total IgE.

Procedure: Each sample and control sample received one SPR IgE strip and the storage bag was tightly closed after extracting the appropriate SPRs. The IgE sign on the gadget was used to choose the test. The calibrator was designated S1 and was tested twice. If the control is being tested, C1 should be used to identify it. Controls and samples were separated in a vortex-type mixer (for serum or plasma separated from particles) and SPRs IgE strips were put into the instrument. Colour labels were scanned to correspond to the scanned symbol on the SPRs and reagent strips. The equipment conducted all scanning procedures automatically. After pipetting, the flasks were resealed and set to 2-8°C. It took around 30 min to complete the scan.

Ethical consideration: Before conducting the study, ethical permission was received from the ethical and scientific board at Ninevah University in Mosul, Iraq. The research adhered to the Declarations of Helsinki's ethical requirements. Before participation, each participant signed a permission form. All participants were promised that their information would be kept strictly secret and would be accessible to the researcher alone. Blood tests were provided free of charge.

Statistical analysis: The ANOVA with a level of probability of $p \leq 0.05$ was used to compare the means of the counts of White Blood Cells (WBC), neutrophils, lymphocytes, monocytes and eosinophils. The correlation coefficient between vitamin D3 and IgE was investigated. The SPSS 26 was used for all statistical analyses.

RESULTS AND DISCUSSION

Table 1 shows a significant decrease in vitamin D levels Mean±SD 14.17±8.23 in the serum of the study samples compared to the control group Mean±SD 41.28±15.22 at a substantial level 0.000 *when $p \leq 0.05$. Skin exposure to sunlight over a certain period is the primary source of vitamin D synthesis. As a result, there is significant seasonal fluctuation, with concentrations greater towards summer's end than in other seasons. Fatty fish such as salmon and mackerel contain vitamin D3. Other rich sources include eggs, beef and fortified foods such as ghee. It is obtained only from food sources, without fortification[14].

To avoid the most damaging Ultraviolet (UV) rays, it is wise to recommend getting 5-15 min of sunshine 4-6 times each week outside of 10 am and 2 pm. Midday ultraviolet exposure is acceptable when UV-blocking chemicals are used responsibly, especially in the summer. For the same amount of vitamin D production, those with darker skin may need 3-4 times more exposure to sun[15]. As people age, their ability to synthesize cholecalciferol diminishes due to lack of exposure to sunlight, especially when they are sick or unable to move and thus stay indoors for long periods.

Furthermore, people with dark skin produce less vitamin D3 due to sun exposure than people with light skin. Intestinal disorders can lead to a decrease in the absorption of vitamin D3. The most important of these disorders are diseases of the small intestine, including celiac disease, inflammatory bowel disease and small intestine resection, all of which can lead to vitamin D3 deficiency[16]. Other conditions that can have the same effect include pancreatic problems and blockage of the bile ducts (primary biliary cirrhosis).

The results showed a significant decrease in the total number of neutrophil cells and, on the contrary, a significant increase in the total number of eosinophil cells at a significant level of $p \leq 0.05$, as shown in Table 2.

Several studies have demonstrated that low vitamin D levels are associated with an increased risk of infections and autoimmune illnesses due to molecular mimicry[17]. Vitamin D3 has been shown to suppress monocyte development into dendritic cells and reduce IL-12 production[18]. Natural killer cell activity, degranulation and inflammatory cytokine production are regulated by vitamin D3. This might indicate the value of vitamin D3 therapy in cancer patients[19]. Vitamin D3 modulates intracellular Toll-like Receptors (TLRs) differently,

Table 1: Comparison of vitamin D3 levels in study samples with control

ng/mL	Sample	Sample N	Mean±SD (ng/mL)	Extreme value (ng/mL)	p-value
D3	Samples	30	14.17±8.23	33.7/8.1	0.000*
	Control	30	41.28±15.22	63/20	

*p<0.05

Table 2: Comparison of some immunological parameters in study samples with control

Cell/mm^3	Sample	Sample N	Mean±SD (cell/mm^3)	Extreme value (cell/mm^3)	p-value
WBC count	Samples	30	7207±1572	10000-4600	0.187
	Control	30	8064±1768	12000-5200	
Neutrophils	Samples	30	4359±1326	5660-2862	0.04*
	Control	30	5401±1280	7200-2808	
Lymphocytes	Samples	30	2143±484	2880-1145	0.954
	Control	30	2156±679	3600-1152	
Monocytes	Samples	30	466±114	662-302	0.606
	Control	30	430±231	1080-216	
Eosinophils	Samples	30	237±158	507-14	0.001*
	Control	30	75±2727	120-61	

*p≤ 0.05

Table 3: Comparison of IgE levels in AR patients with control

ng/mL	Sample	Sample N	Mean±SD (ng/mL)	Extreme value (ng/mL)	p-value
IgE	Samples	30	150.58±100.26	397.06-5.64	0.002*
	Control	30	32.50±12.58	60.36-23.12	

*p≤ 0.05

downregulating TLR9 while leaving TLR3 alone. Less IL-6 is released as a result of lower TLR9 expression. This emphasizes the link between a lack of vitamin D3 and an increased risk of developing autoimmune disorders[20].

Vitamin D3 affects B and T cells. According to several research, vitamin D3 reduces the efficacy of B cells, resulting in lower autoantibody synthesis via B cell death[21]. Furthermore, vitamin D3 may decrease T helper (Th) cell differentiation and encourage a more tolerant immunological response than proinflammatory ones[22]. Vitamin D can prevent the production of pro-inflammatory Th1, Th9[23] and Th22 cytokines while promoting the production of anti-inflammatory Th2 cytokines. As a result, research supports the hypothesis that vitamin D3 lowers the risk of acquiring immunological illnesses[24], indicating that vitamin D influences how the immune system adapts. The VD3R is not present in inactive B lymphocytes. It is only upregulated when mitogens stimulate B lymphocytes for proliferation[25]. Eosinophils express the VD3 receptor and 1,25$(OH)_2$D3 increases the expression of the inhibitory chemokine receptor CXCR4 on the surface of eosinophils. Additionally, vitamin D3 decreases eosinophil necrosis and the release of cytolytic peroxidase[26], IgE synthesis and the expression of interleukin-10, an anti-inflammatory cytokine.

Some studies have shown a link between vitamin D and the development of allergy symptoms. Vitamin D3 levels in the blood were inversely associated with developing asthma and systemic diseases[27,28]. In other words, research has demonstrated that supplementing with vitamin D3 lowers inflammation of the bronchial tubes and bronchi. Regarding other allergic disorders, vitamin D3 deficiency raises the risk of atopic dermatitis and AR[29,30].

The increase in the number of eosinophils may indicate the presence of an allergic immune reaction, which is the first type of allergic reaction (anaphylactic type)[31]. The appearance of these reactions suggests the presence of an inflammatory condition, which AR represents.

The results showed a significant increase in the levels of IgE in the serum of the AR patients Mean±SD 150.58±100.26 compared with control Mean±SD 32.50±12.58 at a significant level 0.002 when $p \leq 0.05$, as shown in Table 3.

The pandemic spread of asthma and associated allergy conditions is a global public health issue. Many studies have revealed that lacking vitamin D3 increases the risk of developing asthma and allergy symptoms. Compared to the control sample, the present study revealed that most persons with AR in Mosul have a deficit in vitamin D3 levels. This was similar to findings from studies of Americans[32].

According to several epidemiological research, vitamin D3 insufficiency is connected with an increased risk of asthma and allergy symptoms[33]. However, these research studies could not provide strong support for these conclusions[34]. According to an Australian study, no link exists between vitamin D3 insufficiency and asthma or allergies in adults[35]. This suggests that the prevalence of vitamin D3 deficiency in the general population is unexpectedly high. It was noted that

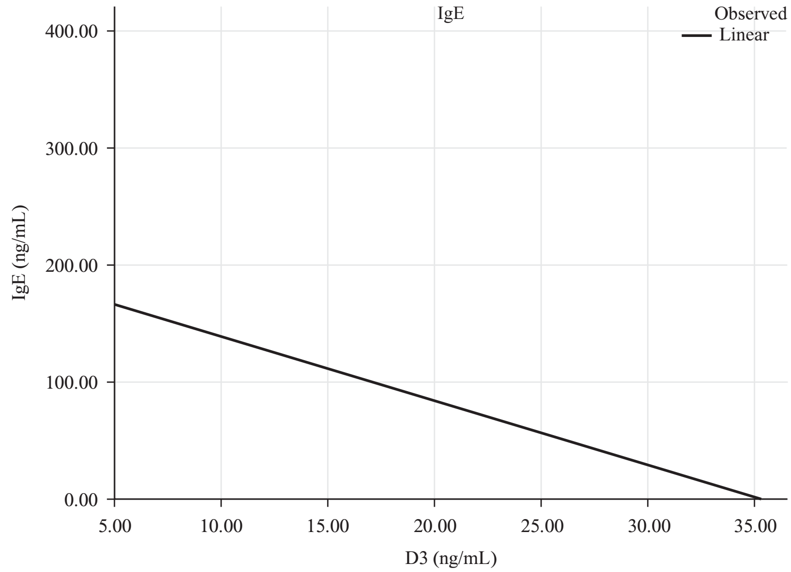

Fig. 1: Regression analysis of the effect of vitamin D3 concentration on IgE concentration in patients with AR

Table 4: Regression analysis of the effect of vitamin D3 concentration on IgE concentration in patients with AR

	Dependent variable: IgE						
	Model summary					Parameter estimates	
Equation	R^2	F	df_1	df_2	Significance	Constant	b_1
Linear	0.58	11.393	1	8	0.010	23.309	-0.056

Independent variable is vitamin D_3, b_1: Regression coefficient, F: Calculated F-value and R^2: Coefficient of clarifications

vitamin D3 deficiency is common even in hot and sun-rich places worldwide and that vitamin D3 supplements and healthy diets were insufficient to prevent deficiency[36]. This reveals that both vitamin D3 deficiency and the occurrence of allergies and asthma are common in the general population and it lends credence to the hypothesis that vitamin D3 levels may impact the risk of acquiring allergies and asthma. The rise in allergy problems is unmistakably linked to environmental and lifestyle factors brought about by industrialization and the progressive westernization of society[37]. According to the web, factors affecting vitamin D status include sun exposure, outdoor activity, food, usage of nutritional supplements, latitude, season, age and skin tone. The study sample showed the subjects had lower physical activity levels and sun exposure. The study participants also had varying degrees of asthma and AR[38].

The results showed in the regression coefficient, there is an inverse and significant effect of vitamin D3 concentration on serum IgE levels, which is significant in terms of the p-value, which appeared equal to 0.010. By observing the value of the R^2 coefficient of clarifications, it is clear that the concentration of D3 causes 58% of the changes in IgE levels and 42% of the changes in IgE are attributed to other random variables that were not included in the regression model as shown in Table 4 and Fig. 1.

According to a recent study, children with asthma had IgE levels much higher than those of normal children and their vitamin D3 levels were significantly lower than those of normal patients. These differences were significant at p 0.05. This explains why a Th1/Th2 cytokine imbalance also causes asthma. A low amount of vitamin D will lessen the inhibitory impact, causing an excess of Th2 cytokines and, ultimately, an increase in the incidence of asthma[39].

The inhibition of autoimmune disorders is thought to be mediated by vitamin D3. In experimental investigations, vitamin D3 has been demonstrated to boost IL-10 production, stimulate regulatory T cells and suppress Th2 and Th17 immunological responses. These effects may all assist in reducing IgE levels[40].

One epidemiological study showed an inverse relationship linking the increase in IgE levels as a result of allergic asthma in adults with a decrease in vitamin D3 levels and their results were consistent with the results of the current study. It is unknown, though, whether vitamin D3 treatment lowers total or allergen-specific IgE levels in adult asthmatics with low vitamin D levels[41]. Patients with AR who are vitamin D deficient can reduce their AR symptoms and enhance their quality of life by taking vitamin D supplements[42]. Similarly, research found that providing vitamin D supplements to individuals deficient in the vitamin combined with usual therapy dramatically lowers asthma flare-ups[43]. One sufficiently robust, well-matched research found that individuals with vitamin D deficiency had a 24-fold increased risk of developing severe AR compared to those with normal levels, supporting the use of vitamin D supplements in AR patients. As a result, the same research advised AR patients to take vitamin D supplements[44,45].

This type of study is a new step in the search for the origin of the appearance of the allergic condition in these patients from the beginning compared to other people. There may be many physiological, nutritional and hormonal reasons that led to the development of this condition. The application of the results of the study also provides an understanding of the treatment of this condition by giving doses of vitamin D3 according to the individual's need until the emergence of the allergic condition is controlled. One of the most prominent limitations that the current study suffers from is the difficulty in convincing patients that it is one of the most important causes of allergic rhinitis. Lack of exposure to the sun or not taking vitamins, including D3, maybe to control the medical condition, as the patient usually always requests quick treatment and treats the allergic condition and does not accept certain long-term nutritional courses.

CONCLUSION

The current investigation found that individuals with AR had lower levels of vitamin D3. Additionally, an inverse linear relationship appeared that linked the effect of the decrease in vitamin D3 levels to an increase in IgE levels with an impact of 58% through the linear regression relationship. The current study also provides fertile ground for following up on the causes of the development of allergic rhinitis, far from traditional studies that show the direct cause of the infection, ignoring the role played by the physiological, nutritional and immunological factors that ultimately lead to the emergence of allergic rhinitis.

SIGNIFICANCE STATEMENT

The current study reveals the extent of the decrease in vitamin D3 levels on some immune variables, as it helps researchers show the adverse effects of this decrease on the development of AR. Therefore, this study will provide specialists with a new field in allergy diseases, AR and asthma. It will help them determine the most important factors causing these pathological conditions and effectively allocate treatment by identifying vitamin D3 deficiency in these patients.

REFERENCES

1. Small, P., P.K. Keith and H. Kim, 2018. Allergic rhinitis. Allergy Asthma Clin. Immunol., Vol. 14. 10.1186/s13223-018-0280-7.
2. Li, Q., Q. Zhou, G. Zhang, X. Tian and Y. Li *et al*., 2022. Vitamin D supplementation and allergic diseases during childhood: A systematic review and meta-analysis. Nutrients, Vol. 14. 10.3390/nu14193947.
3. Bhardwaj, B. and J. Singh, 2021. Efficacy of vitamin D supplementation in allergic rhinitis. Indian J. Otolaryngol. Head Neck Surg., 73: 152-159.
4. Fu, H., Y. Li, H. Huang and D. Wang, 2022. Serum vitamin D level and efficacy of vitamin D supplementation in children with atopic dermatitis: A systematic review and meta-analysis. Comput. Math. Methods Med., Vol. 2022. 10.1155/2022/9407888.
5. Ao, T., J. Kikuta and M. Ishii, 2021. The effects of vitamin D on immune system and inflammatory diseases. Biomolecules, Vol. 11. 10.3390/biom11111624.
6. Hayashi, H., M. Okamatsu, H. Ogasawara, N. Tsugawa, N. Isoda, K. Matsuno and Y. Sakoda, 2020. Oral supplementation of the vitamin D metabolite 25(OH)D_3 against influenza virus infection in mice. Nutrients, Vol. 12. 10.3390/nu12072000.
7. Jorde, R. and J. Kubiak, 2018. No improvement in depressive symptoms by vitamin D supplementation: Results from a randomised controlled trial. J. Nutr. Sci., Vol. 7. 10.1017/jns.2018.19.
8. Young, A.R., K.A. Morgan, G.I. Harrison, K.P. Lawrence, B. Petersen, H.C. Wulf and P.A. Philipsen, 2021. A revised action spectrum for vitamin D synthesis by suberythemal UV radiation exposure in humans *in vivo*. Proc. Natl. Acad. Sci. USA, Vol. 118. 10.1073/pnas.2015867118.
9. Ghaseminejad-Raeini, A., A. Ghaderi, A. Sharafi, B. Nematollahi-Sani, M. Moossavi, A. Derakhshani and G.A. Sarab, 2023. Immunomodulatory actions of vitamin D in various immune-related disorders: A comprehensive review. Front. Immunol., Vol. 14. 10.3389/fimmu.2023.950465.
10. Mazur, A., P. Frączek and J. Tabarkiewicz, 2022. Vitamin D as a nutri-epigenetic factor in autoimmunity-A review of current research and reports on vitamin D deficiency in autoimmune diseases. Nutrients, Vol. 14. 10.3390/nu14204286.
11. Voltan, G., M. Cannito, M. Ferrarese, F. Ceccato and V. Camozzi, 2023. Vitamin D: An overview of gene regulation, ranging from metabolism to genomic effects. Genes, Vol. 14. 10.3390/genes14091691.

12. Seidman, M.D., R.K. Gurgel, S.Y. Lin, S.R. Schwartz and F.M. Baroody *et al*., 2015. Clinical practice guideline: Allergic rhinitis. Otolaryngol. Head Neck Surg., 152: S1-S43.
13. Ringe, J.D. and C. Kipshoven, 2012. Vitamin D-insufficiency: An estimate of the situation in Germany. Dermato-Endocrinol., 4: 72-80.
14. de la Puente Yagüe, M., L.C. Yurrita, M.J.C. Cabañas and M.A.C. Cenzual, 2020. Role of vitamin D in athletes and their performance: Current concepts and new trends. Nutrients, Vol. 12. 10.3390/nu12020579.
15. Raymond-Lezman, J.R. and S.I. Riskin, 2023. Benefits and risks of sun exposure to maintain adequate vitamin D levels. Cureus, Vol. 15. 10.7759/cureus.38578.
16. Dominguez, L.J., M. Farruggia, N. Veronese and M. Barbagallo, 2021. Vitamin D sources, metabolism, and deficiency: Available compounds and guidelines for its treatment. Metabolites, Vol. 11. 10.3390/metabo11040255.
17. Sîrbe, C., S. Rednic, A. Grama and T.L. Pop, 2022. An update on the effects of vitamin D on the immune system and autoimmune diseases. Int. J. Mol. Sci., Vol. 23. 10.3390/ijms23179784.
18. Gallo, D., D. Baci, N. Kustrimovic, N. Lanzo and B. Patera *et al*., 2023. How does vitamin D affect immune cells crosstalk in autoimmune diseases? Int. J. Mol. Sci., Vol. 24. 10.3390/ijms24054689.
19. Ota, K., S. Dambaeva, M.W.I. Kim, A.R. Han and A. Fukui *et al*., 2015. 1,25-Dihydroxy-vitamin D3 regulates NK-cell cytotoxicity, cytokine secretion, and degranulation in women with recurrent pregnancy losses. Eur. J. Immunol., 45: 3188-3199.
20. Ojaimi, S., N.A. Skinner, B.J.G. Strauss, V. Sundararajan, I. Woolley and K. Visvanathan, 2013. Vitamin d deficiency impacts on expression of toll-like receptor-2 and cytokine profile: A pilot study. J. Transl. Med., Vol. 11. 10.1186/1479-5876-11-176.
21. Rolf, L., A.H. Muris, R. Hupperts and J. Damoiseaux, 2016. Illuminating vitamin D effects on B cells-The multiple sclerosis perspective. Immunology, 147: 275-284.
22. Martens, P.J., C. Gysemans, A. Verstuyf and C. Mathieu, 2020. Vitamin D's effect on immune function. Nutrients, Vol. 12. 10.3390/nu12051248.
23. Yang, C.Y., P.S.C. Leung, I.E. Adamopoulos and M.E. Gershwin, 2013. The implication of vitamin D and autoimmunity: A comprehensive review. Clin. Rev. Allergy Immunol., 45: 217-226.
24. Dupuis, M.L., M.T. Pagano, M. Pierdominici and E. Ortona, 2021. The role of vitamin D in autoimmune diseases: Could sex make the difference? Biol. Sex Differ., Vol. 12. 10.1186/s13293-021-00358-3.
25. Aranow, C., 2011. Vitamin D and the immune system. J. Invest. Med., 59: 881-886.
26. Hiraguchi, Y., H. Tanida, M. Sugimoto, K. Hosoki, M. Nagao, R. Tokuda and T. Fujisawa, 2012. 1,25-Dihydroxyvitamin D_3 upregulates functional C-X-C chemokine receptor type 4 expression in human eosinophils. Int. Arch. Allergy Immunol., 158: 51-57.
27. Mirzakhani, H., A. Al-Garawi, S.T. Weiss and A.A. Litonjua, 2015. Vitamin D and the development of allergic disease: How important is it? Clin. Exp. Allergy, 45: 114-125.
28. Hall, S.C. and D.K. Agrawal, 2017. Vitamin D and bronchial asthma: An overview of data from the past 5 years. Clin. Ther., 39: 917-929.
29. di Gioacchino, M., C. Petrarca, L.D. Valle, R. Mangifesta and F. Santilli, 2023. Is there a rationale for supplementing with vitamin D patients under treatment with allergen immunotherapy? Ann. Med., Vol. 55. 10.1080/07853890.2023.2230864.
30. Podlecka, D., J. Jerzyńska, K. Sanad, K. Polańska, M. Bobrowska-Korzeniowska, I. Stelmach and A. Brzozowska, 2022. Micronutrients and the risk of allergic diseases in school children. Int. J. Environ. Res. Public Health, Vol. 19. 10.3390/ijerph191912187.
31. Qua, C.S., K.B. Peh, K. Saravannan and K.L. Goh, 2021. Vitamin D deficiency causing eosinophilic esophagogastroenteritis and ascites: A rare association. BMJ Case Rep., Vol. 14. 10.1136/bcr-2020-240039.
32. Choi, H.G., S.Y. Kim, Y.H. Joo, H.J. Cho, S.W. Kim and Y.J. Jeon, 2022. Incidence of asthma, atopic dermatitis, and allergic rhinitis in Korean adults before and during the COVID-19 pandemic using data from the Korea National Health and Nutrition Examination Survey. Int. J. Environ. Res. Public Health, Vol. 19. 10.3390/ijerph192114274.
33. Han, Y.Y., E. Forno and J.C. Celedón, 2017. Vitamin D Insufficiency and asthma in a US nationwide study. J. Allergy Clin. Immunol.: Pract., 5: 790-796.e1.
34. Tibrewal, C., N.S. Modi, P.S. Bajoria, P.A. Dave and R.K. Rohit *et al*., 2023. Therapeutic potential of vitamin D in management of asthma: A literature review. Cureus, Vol. 15. 10.7759/cureus.41956.
35. Williamson, A., A.R. Martineau, A. Sheikh, D. Jolliffe and C.J. Griffiths, 2023. Vitamin D for the management of asthma. Cochrane Database Syst. Rev., Vol. 2. 10.1002/14651858.CD011511.pub3.
36. Aparna, P., S. Muthathal, N. Baridalyne and K.G. Sanjeev, 2018. Vitamin D deficiency in India. J. Fam. Med. Primary Care, 7: 324-330.
37. Bener, A., M.S. Ehlayel, H.Z. Bener and Q. Hamid, 2014. The impact of vitamin D deficiency on asthma, allergic rhinitis and wheezing in children: An emerging public health problem. J. Fam. Community Med., 21: 154-161.
38. Rueter, K., A.P. Jones, A. Siafarikas, P. Chivers, S.L. Prescott and D.J. Palmer, 2021. The influence of sunlight exposure and sun protecting behaviours on allergic outcomes in early childhood. Int. J. Environ. Res. Public Health, Vol. 18. 10.3390/ijerph18105429.

39. Zhao, R., W. Zhang, C. Ma, Y. Zhao and R. Xiong *et al*., 2021. Immunomodulatory function of vitamin D and its role in autoimmune thyroid disease. Front. Immunol., Vol. 12. 10.3389/fimmu.2021.574967.
40. Nair, R. and A. Maseeh, 2012. Vitamin D: The "sunshine" vitamin. J. Pharmacol. Pharmacother., 3: 118-126.
41. Rosser, F.J., Y.Y. Han, E. Forno, L.B. Bacharier and W. Phipatanakul *et al*., 2022. Effect of vitamin D supplementation on total and allergen-specific IgE in children with asthma and low vitamin D levels. J. Allergy Clin. Immunol., 149: 440-444.E2.
42. Pludowski, P., 2023. Supplementing vitamin D in different patient groups to reduce deficiency. Nutrients, Vol. 15. 10.3390/nu15173725.
43. Liu, M., J. Wang and X. Sun, 2022. A meta-analysis on vitamin D supplementation and asthma treatment. Front. Nutr., Vol. 9. 10.3389/fnut.2022.860628.
44. Walsh, J.B., D.M. McCartney, É. Laird, K. McCarroll and D.G. Byrne *et al*., 2022. Title: Understanding a low vitamin D state in the context of COVID-19. Front. Pharmacol., Vol. 13. 10.3389/fphar.2022.835480.
45. Partap, U., K.K. Sharma, Y. Marathe, M. Wang and S. Shaikh *et al*., 2023. Vitamin D and zinc supplementation to improve treatment outcomes among COVID-19 patients in India: Results from a double-blind randomized placebo-controlled trial. Curr. Dev. Nutr., Vol. 7. 10.1016/j.cdnut.2023.101971.