https://doi.org/10.48047/AFJBS.6.14.2024.3577-3587

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Role of Vitamin D Deficiency in Patients with Interstitial Lung Diseases

Naglaa Bakry Ahmed Elkhatib[1], Esmat Ali Ali Abd-ElNaby[2], Samah Selim Abd-ElNaiem Selim[3], Walaa Ahmed Mohammed Mohammed[4], Rania Othman Ibrahim Ibrahim[5]

[1] Assistant professor of Chest diseases, Faculty of Medicine, Cairo University, Cairo, Egypt.

[2] Professor of chest diseases, Faculty of Medicine, Cairo University, Cairo, Egypt

[3] professor of Chest diseases, Faculty of Medicine, Cairo University, Cairo, Egypt

[4] Assistant professor of Chemical pathology, Faculty of Medicine- Cairo University, cairo, Egypt

[5] M.Sc. Chest diseases, Faculty of Medicine, Cairo University, Cairo, Egypt

Corresponding author: Naglaa Bakry Ahmed Elkhatib.

Email: naglaa.bakry@kasralainy.edu.eg

Article History

Volume 6, Issue 14, 2024

Received: 03 July 2024

Accepted: 10 August 2024

doi: 10.48047/AFJBS.6.14.2024.3577-3587

Abstract:

Background: Interstitial lung diseases (ILD) are chronic inflammation and fibrosis of lung tissue, affecting interstitial, alveolar, and vascular areas of the lungs.

Aim: To assess the effect of vitamin D (VD) supplementation in treating ILD cases, excluding connective tissue-associated interstitial lung diseases

Patients and methods: This investigation was a randomized controlled trial involving 104 cases with interstitial lung disease who looked for evaluation and therapy at the Chest Department in collaboration with the Chemical Pathology Department at Kasr Al-Ainy Hospital, Cairo University. The investigation has been performed from February 2019 to November 2019.

Results: Following three months of VD supplement, the serum VD level significantly rose from 5.7 to 18.5 (nanogram per milliliter), with a with a P-value less than 0.001. Regarding the score of dyspnea, it significantly decreased from 3 to 2, P < 0.001. The spirometery readings of the cases showed improvement at the level of large airways, as both FEV1% and FVC were significantly enhanced (P = 0.02 and 0.004), correspondingly, while at the small airways level, the improvement failed (P = 0.3). Considering the patient's ability to do a 6-minute walk test (6MWT), it significantly improved and subsequently the patient's oxygenation (P = < 0.001, 0.01 and 0.03), respectively.

Conclusion: Vitamin D supplementation improved the score of dyspnea; it significantly decreased from three to two, considering the patient's ability to do 6MWT. It also significantly enhanced and subsequently improved the patient's oxygenation after vitamin D supplementation.

Keywords: Interstitial lung diseases, Vitamin D, 6MWT

1. Introduction

VD is a steroid hormone that has several impacts, such as modifying the immune system, remodeling lung tissue, & promoting health of bone. The occurrence of autoimmune disorders has been related to a lack of vitamin D **(1)**.

Interstitial lung disease (ILD) is being increasingly recognized as a significant factor contributing to illness and death early **(2)**.

Interstitial lung disorders, also called diffuse parenchymal lung diseases (DPLD), are characterized by persistent and widespread inflammation and fibrosis of the lung tissue, affecting the interstitial, alveolar, and vascular regions. DPLD can be categorized into two categories: idiopathic interstitial pneumonia (IIP) and ILD other than IIP **(3)**.

ILD is a condition that is distinguished by the progressive fibrosis of the lung, which results in reduced oxygen transfer and restriction. Clinically, the initial symptoms of ILD aren't different and usually include a cough and progressive dyspnea on exertion. These symptoms are sometimes mistakenly given to other illnesses, resulting in a delay in diagnosis and timely treatment **(4).**

Administration of vitamin D or its analogs effectively inhibited the development of fibrosis in the kidneys and liver. The potential cause of this anti-fibrotic impact may be related to the reduction of TGF-B activity. Research has shown that vitamin D can decrease expression of TGF-B1 and attenuate TGF-B1 induced epithelial-mesenchymal transition (EMT) in lung fibroblasts, myocardium, renal tissue, and in cases of lung fibrosis induced by bleomycin **(5)**.

The benefits of VD are correlated with the reversal of the downregulation of vitamin D receptor (VDR) mRNA levels induced by TGFB1. VD may exert its protective impacts by disrupting key kinase-controlled signal transduction pathways that are included in the TGFB1 signaling apparatus **(6)**.

Vitamin D administration may prevent bleomycin-induced lung fibrosis by delaying or suppressing ultrastructural changes, as well as reducing the accumulation of hydroxyproline and limiting the proliferation of myofibroblasts **(7)**.

The purpose of this investigation was to investigate the serum concentration of VD in cases with interstitial lung diseases that have no association with connective tissue disorders. Additionally, the study aimed to assess the effectiveness of VD supplementation in conjunction with the regular therapy strategy for ILD.

Patients and methods

This investigation was a randomized controlled trial involving 104 cases with interstitial lung disorders, specifically sarcoidosis, hypersensitivity pneumonitis, and idiopathic pulmonary fibrosis. The cases have been seen at the Chest Department of Kasr Al-Ainy Hospital, Cairo University, for accurate evaluation and therapy. The investigation has been performed in collaboration with the Chemical Pathology Department from February 2019 to November 2019. Each case that was registered was assigned at random to one of the following groups: Group one, the intervention group, consisted of fifty-two cases with vitamin D deficiency or insufficiency who got both vitamin D supplementation and the standard therapy for ILD. Group two, the control group, consisted of fifty-two cases with vitamin D deficiency or insufficiency who only received the standard therapy for ILD.

Ethical consideration: The investigation was conducted in compliance with the Helsinki Declaration and received approval from the ethical committee of the research of the Faculty of Medicine at Cairo University (investigation number: 104 cases). Prior to their enrollment in the investigation, all subjects were required to provide informed written consent.

Exclusion criteria: cases with disorders such as chronic renal diseases, malignancy, liver disorders, etc. patients unable to do spirometry or 6-MWT, those who were already taking vitamin D supplementation prior to the study, as well as cases with ischemic heart disorder, connective tissue-associated ILD, congestive heart failure, and exacerbation of ILD.

Sample size:

The sample size estimation was conducted based on the comparison of the average distance in the six-minute walk test among patients with interstitial pulmonary fibrosis (IPF) who received VD supplementation and untreated matched cases. This has been chosen as the major outcome measure for our investigation. In a recent publication by **Du Bois et al. (8),** it was stated that the mean ±SD of the six-minute walk test in the untreated group was 392.4 ± 108 meters. We hypothesized that VD administration could result in at least a rise of sixty meters in distance. Therefore, we determined that a minimum sample size of fifty-two cases in each group was necessary to have a sufficient statistical power of eighty percent to reject the null hypothesis at a significance level of $\alpha = 0.05$, utilizing the student's t-test. The sample size estimation has been carried out by G*Power software version 3.1.2 for MS Windows, developed by Franz Faul at Kiel University, Germany.

Methods:

Cases have been identified using the interstitial lung disorder diagnostic algorithm **(9),** which involved a multidisciplinary approach involving laboratory examinations, clinical data, functional assessment, high-resolution CT scans of the chest, as well as lung biopsy when appropriate.

High-resolution computed tomographic scans of the chest (HRCT) by Siemens 16-channel multi-detector computerized tomography (MDCT): The photos have been acquired during the final phase of inspiration and while in the in the supine position, capturing the entire range from the apices to the bases of the lungs. No contrast medium has been administered. The information has been reconstructed using a section thickness of one millimeter and at intervals of ten millimeters for transverse pictures.

Measurement of serum levels of VD:

The standard venipuncture technique has been utilized to obtain a peripheral venous blood sample, which was subsequently centrifuged. Samples that were grossly hemolytic weren't included. The specimens have been refrigerated at minus twenty degrees Celsius if they were held for an extended period or stored at two to eight degrees Celsius for up to forty-eight hours before assaying. The solid-phase enzyme-linked immunosorbent assay (ELISA) has been utilized to quantify the serum vitamin D level. The categorization of 25-OH VD status was proposed in the following ranges by recent literature: Deficiency is defined as a level of zero and ten nanograms per milliliter., insufficiency as ten to thirty nanograms per milliliter, sufficiency as thirty to one hundred nanograms per milliliter, and VD toxicity as over one hundred nanograms per milliliter **(10).**

The therapy that has been received in the examined population is as follows:

For two groups, corticosteroids and immune suppressive medicines (azathioprine and methotrexate) are the standard treatments for interstitial lung diseases, when appropriate.

For the intervention group, VD supplement involves administering two hundred thousand international units of colicalciferol (vitamin D3), also known as Devarol, through an IM injection. The dosage frequency is every two weeks for a duration of three months for cases with a deficient serum VD level (zero and ten nanograms per milliliter) and every month for a duration of three months for cases with an insufficient serum vitamin D level (ten to thirty nanograms per milliliter). Cases who had a blood vitamin D level within the range of thirty to one hundred nanograms per milliliter did not get any vitamin D supplementation. In addition, all cases received a set dose of six hundred milligrams of calcium supplementation orally once daily for a duration of three months.

Follow up in the in the following three months:

A three-month follow-up was conducted for all cases in both the intervention group and the control group. An evaluation was conducted to evaluate the severity of shortness of breath as well as changes in spirometry parameters and the distance covered during the six-minute walk test.

Statistical methods

The information was gathered, tabulated, and statistically analyzed utilizing Minitab 17.1.0.0 for Windows (Minitab Inc., 2013, Pennsylvania, United States of America). All tests were two sided. A p-value of lower than 0.05 has been regarded as significant. Categorical information has been represented as a number and percentage, while continuous data has been represented as SD, mean, or median and IQR. The independent t-test or Mann-Whitney test is utilized to compare 2 groups of continuous data, while the chi-square test is utilized to compare 2 or more groups of categorical data. The paired t-test was utilized to compare the means of two groups prior to and following the intervention. The direction of the association is represented by the sign before the "r" in the Pearson correlation coefficient, which is utilized to calculate a linear relationship between two or more numerical variables. The impact of factors on serum vitamin D in serum is estimated using multiple linear logistic regressions. The sign before "coefficient" indicates the direction of the linear relationship.

Results

Table (1): Baseline characteristics of intervention & control groups.

Variable	**Intervention group (number=52)**		**Control group (number =52)**		**P**
	(mean±SD) / (n, %)		**(mean±SD) / (n, %)**		
Age	46.2	7.5	48.66	5.4	0.32$^{\$}$
Sex					
• **Female**	41	78.84	41	78.84	1$^{\#}$
• **Male**	11	25.16	11	25.16	
BMI	29.9	5.85	33.07	7.77	0.07$^{\$}$
Dyspnea Score	3.031	0.538	2.875	0.609	0.23$^{\$}$

Diagnosis					
• **HP**	24	46.16	24	68.75	1[#]
• **Sarcoid**	17	32.69	17	25	
• **UIP/IPF**	11	21.15	11	6.25	
FVC %	58%	22%	60%	23%	0.76[$]
FEV1 %	56%	22%	58%	23%	0.7[$]
FEV1/FVC %	81%	16%	81%	10%	0.95[$]
MEF25%	46%	26%	45%	32%	0.89[$]
6MWT	259.9	76.1	285.1	82.1	0.2[$]
Basal So2 in 6MWT %	91%	8%	93%	4%	0.14[$]
Post 6MWT SO2 %	83%	12%	88%	7%	0.07[$]
O2 desaturation in 6MWT %	6%	(3-10) %	5%	(2-7) %	0.12[$$]
VD (ng/L) (median, IQR)	5.7	(3.6-8.7)	7.2	(4.4-15.7)	0.08[$$]

N: number, SD: Stander deviation, IQR: inter quartile range, $: independent t test, $$: Mann Whitney test, #: Chi square test, P considered significant if < 0.05. VD: vitamin D

In comparing the two groups as regarding demographic, clinical and VD level, the matching pattern was the finding, as there non-significant statistical variation has been observed in among the groups (Table 1).

Table (2): Serum Vitamin D level, status and calcium among all patients

	Total (n=104)	
	(Mean± SD) (N, %)	
Variable		
• **Vit.D (ng/mL)**	8.53	6.29
• **Ca (mg/dL)**	8.88	0.67
VD status		
• **Deficient**	76	73.08%
• **Insufficient**	28	26.92%

N: number, SD: Stander deviation

All patients that included in the study suffered from VD deficiency and insufficiency (73.08 and 26.92%) respectively, with mean VD level in serum (8.53 ± 6.29). The serum ca level was in the normal average. (Mean ± SD = 8.88- 0.67mg/dl) (Table 2).

Table (3): Linear regression analysis of factors affecting vitamin D level in patients with ILD

	Coefficient	**SE**	**P**
Variable			

• **Age**	0.15	0.10	0.13
• **BMI**	0.10	0.13	0.44
• **Sex (male)**	-0.80	2.13	0.71
• **FVC**	-0.03	0.04	0.40
• **6MWT**	0.01	0.01	0.49
Diagnosis			
• **Sarcoid**	1.01	2.02	0.62
• **UIP/IPF**	5.93	3.38	0.09
Steroid use (yes)	11.64	4.72	0.02

SE: stander error, P considered significant if < 0.05, the singe before coefficient denote the direction of the relationship.

Neither age, BMI, sex, FVC, 6MWT nor ILD type affect the Vitamin D (VD) level in serum, and only steroid use was significantly affecting the level of VD in serum in correspondent way, (P = 0.02) (Table 3).

Table (4): Statistical analysis was conducted on the determined parameters in the intervention group both prior to & following a three-month period of vitamin D administration.

Variable	**Before (n=49)**		**After (n=49)**		**95% CI**	**P**
	(mean±SD)		**(mean±SD)**			
Dyspnea Score	3.03	0.54	1.91	1.00	(0.728,1.522)	< 0.001
FVC % predicted	60%	22%	68%	20%	(-13.35,-2.72)	0.004
FEV1 % predicted	56%	23%	62%	20%	(-0.1134,-0.0097)	0.02
FEV1/FVC %	80%	16%	81%	11%	(-0.0643,0.0497)	0.70
MEF25% predicted	41%	23%	37%	22%	(-0.0470,0.1310)	0.30
6MWT Distance	257.30	74.50	299.50	84.10	(-62.32,-22.02)	<0.001
Basal So2 in 6MWT %	0.91	0.08	0.93	0.04	(-0.04119,-0.00569)	0.01
O2 desaturation in 6MWT %	6%	(3-10) %	5%	(0-7)%	(-0.00001,0.04999)	0.03
VD (ng/L) (median, IQR)	5.7	(3.6-8.7)	18.5	(15-22)	(-14.900,-10.601)	< 0.001

SD: stander deviation, IQR: inter quartile range, ^: Paired t test, $$: Mann Whitney test, P considered significant if P < 0.05.

Following three months of VD supplement, the level of serum VD level significantly rose from 5.7 - 18.5 (nanogram per milliliter), P-value less than 0.001. Regarding the score of dyspnea, it significantly reduced from 3 to 2, P < 0.001. About spirometery reading of cases showed improvement at the level of large airways as both FEV1%and FVC were significantly enhanced, (P=0.02 and 0.004) correspondingly while at the level of small airways, the improvement failed, P= 0.3. Considering the patient's ability for doing 6MWT, it significantly improved and subsequently the patient's oxygenation, P = < 0.001, 0.01 & 0.03) respectively (Table 4).

Table (5): Correlation among serum VD levels changes and changes in both spirometery readings and 6-MWT-distance in group of intervention

Variable	**Vitamin D level changes**

	r	P*
FVC% change	0.41	0.03
FEV1 %change	0.50	0.01
FEV1/FVC% change	0.21	0.27
MEF25% change	0.37	0.05
6MWT distance change	0.12	0.55

*: Person correlation coefficient

There is a positive correlation between the magnitude of improvements in level of VD before and following supplementation and the improvement in FEV1, FVC, and MEF25% (r= 0.5, 0.41, & 0.37; p-values of 0.01, 0.03, & 0.05, respectively). While the changes of VD were insignificantly correlated with changes in 6MWT, P = 0.55 (Table 5).

Table (6): Comparison between changes in spirometry and 6MWT parameters in the intervention & control groups

Variable	**Case changes (n=49)**		**Control changes (n=51)**		**P**
	(median, IQR)		**(median, IQR)**		
FVC %	4%	(0-17) %	1%	(-6-4) %	0.02$$
FEV1 %	5%	(-4-17) %	2%	(-5-7) %	0.14$$
FEV1/FVC %	0%	(-7-4) %	1%	(-2-3) %	0.21$$
MEF25%	-7%	(-16-7) %	4%	(-9-10) %	0.19$$
6MWTdistance	30	(0-60)	0	(-30-30)	0.004$$

N: number, IQR: inter quartile range, $$: Mann Whitney test, P considered significant if < 0.05.

Considering the changes in FVC%, it showed significantly higher changes in case than in control group, P =0.02, while FEV1, FEV1/FVC% and MEF25%, there were insignificant statistical difference in between the two groups. Regarding 6MWT, the changes was significantly greater in case group than in control one, P = 0.004 (Table 6).

Discussion

In comparing the two groups as regards demographic, clinical, and VD level, the matching pattern was the finding, as there was non-significant statistical variation among the two groups.

In our research, we demonstrated that vitamin D deficiency and insufficient levels (73.08 and 26.92%) were highly prevalent in all patients included in our study, with a mean vitamin D level in serum (8.53 ± 6.29)

In their investigation, **Hagaman et al. (11)** showed that VD deficiency & insufficiency were frequent among cases with ILD. They also discovered that these deficiencies have been related to the existence of an underlying CTD, regardless of other factors that could affect the results in this group of cases.

Neither age, BMI, sex, FVC, 6MWT nor ILD type affect the vitamin D (VD) level in serum, and only steroid use significantly affects the level of VD in serum in a similar way (P = 0.02).

Elnady et al. (12) found that there were significant negative associations among serum VD levels & both age and the length of steroid medication. Linear regression analysis revealed that patients' age and the length of steroid therapy were statistically significant predictors of low serum VD levels (with p-values of 0.045 and 0.01, respectively).

Mulrennan et al. (13) discovered that adjusting for sex was important in their investigation. They observed that the average VD level was greater in males compared to females. Additionally, they found that the largest frequency of VD deficiency was among women who were not using vitamin D supplements.

Following a three-month period of VD administration, the serum vitamin D level increased significantly from 5.7 to 18.5 (nanograms per milliliter), with a p-value less than 0.001. The dyspnea score shown declined significantly from three to two, with a statistically significant difference (P < 0.001). The spirometry readings of the patients demonstrated a significant enhancement in the function of the large airways, with both forced vital capacity & forced expiratory volume in one second showing significant increases (P = 0.004 and 0.02, respectively). However, there was no observed improvement in the function of the small airways, as indicated by an absence of statistical significance (P = 0.3). Upon evaluating the patient's capacity to perform the six-minute walk test, there was a significant and statistically significant improvement. This improvement was subsequently reflected in the case's oxygenation levels, with p-values of less than 0.001, 0.01, and 0.03, respectively.

Gilbert et al. (14) discovered that the correlation between VD deficiency and decreased lung function may be influenced by the impact of VD on calcium levels. As a direct result of VD deficiency, the vital capacity and total lung capacity were observed to decrease as the number of thoracic vertebral fractures increased.

This doesn’t come in agreement with our study, as in our study, the serum ca level in all studied patients (vitamin D deficient or insufficient) was in the normal range. (mean ± SD = 8.8–0.6 mg/dl).

In their study**, Sutherland et al. (15)** found that a lack of vitamin D negatively affects lung function, enhances the sensitivity of the airways, and reduces the effectiveness of glucocorticoid treatment. This comes in agreement with our study result as regard to the significant improvement of FVC & FEV1% after vitamin supplementation (P = 0.004 and 0.02).

Monadi et al. (16) corroborated our investigation findings in COPD cases, demonstrating a significant association among vitamin D levels and lung function. The research findings suggest that there is a correlation between low levels of serum 25(OH)D and reduced FEV1 in cases with COPD.

In their study, **Foong et al. (17)** illustrated that a lack of vitamin D led to increased airway hyperresponsiveness in female mice of mature age. Additionally, there was a corresponding increase in the mass of airway smooth muscle (ASM), along with a decrease in lung volume, lower volume of lung tissue, alveolar septa, and air within the lung tissue, diminished alveolar surface area, and modified lung structure. These changes have a significant impact on lung function, particularly on FVC and forced expiratory volume in one second.

Considering the changes in FVC%, it showed significantly greater changes in the case than in the control group (P = 0.02), while for FEV1, FEV1/FVC% and MEF25%, there were insignificant statistical differences between the two groups. As regarding 6MWT, the changes were significantly greater in the case group than in the control group (P = 0.004).

There is a positive correlation between the degree of improvements in vitamin D level prior to and following supplementation and the improvement in FEV1, FVC, and MEF25% (correlation coefficients of 0.5, 0.41, and 0.37; p-values of 0.01, 0.03, and 0.05, respectively). The increases in VD showed no significant correlation with alterations in 6MWT, with a p-value of 0.55.

Sluyter et al. (18) showed that monthly, high-dose vitamin D supplementation did not affect lung function. However, there was a positive correlation between the change of serum vitamin D and the change of FEV1% . In our study, we demonstrated that the larger the changes in vitamin D level in patients with ILD before and after supplementation, the more the improvement in FVC%, FEV1% and MEF 25% while the changes of vitamin D was positively correlated with changes in 6-MWT although no statistical significance was detected.

Conclusion

A significant correlation is present among levels of VD (25-hydroxyvitamin D) and lung function tests, specifically FEV1 and FVC. The administration of Vitamin D resulted in an enhancement of the dyspnea score, with a significant reduction from three to two. Furthermore, there was a significant rise in the patient's ability to do the 6-minute walk test, as well as an improvement in the case's oxygenation levels following VD supplementation.

References

1. Sundar IK, Rahman I. Vitamin D and susceptibility of chronic lung diseases: role of epigenetics. Frontiers in pharmacology. 2011 Aug 30;2:50.
2. Johannson KA, Hambly N, Assayag D, Ryerson CJ. Update in the diagnostic approach to fibrotic interstitial lung disease. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine. 2019 Jul 3;3(3):155-9.
3. Mehrad B, Strieter RM. Fibrocytes and the pathogenesis of diffuse parenchymal lung disease. Fibrogenesis & tissue repair. 2012 Jun 6;5(Suppl 1):S22.
4. Peros-Golubicic T, Sharma OP. Clinical atlas of interstitial lung disease. Springer Science & Business Media; 2006 Nov 23.
5. Kabel AM, Abd Elmaaboud MA, Atef A, Baali MH. RETRACTED: Ameliorative potential of linagliptin and/or calcipotriol onbleomycin-induced lung fibrosis: In vivo and in vitro study.

6. Tzilas V, Bouros E, Barbayianni I, Karampitsakos T, Kourtidou S, Ntassiou M, Ninou I, Aidinis V, Bouros D, Tzouvelekis A. Vitamin D prevents experimental lung fibrosis and predicts survival in patients with idiopathic pulmonary fibrosis. Pulmonary Pharmacology & Therapeutics. 2019 Apr 1;55:17-24.
7. Zhang Z, Yu X, Fang X, Liang A, Yu Z, Gu P, Zeng Y, He J, Zhu H, Li S, Fan D. Preventive effects of vitamin D treatment on bleomycin-induced pulmonary fibrosis. Scientific reports. 2015 Dec 2;5(1):17638.
8. Du Bois RM, Albera C, Costabel U, Bradford WZ, Kartashov A, Noble PW, Szwarcberg J, Thomeer M, Valeyre D, Weycker D, King, Jr TE. 6-minute walk test distance (6MWD) is a reliable, valid, and responsive outcome measure that predicts mortality in patients with IPF. InA23. IDIOPATHIC PULMONARY FIBROSIS: EPIDEMIOLOGY, BIOMARKERS, AND OUTCOMES 2010 May (pp. A1103-A1103). American Thoracic Society.
9. Saha K. Interstitial lung disease: Diagnostic approach. The Journal of Association of Chest Physicians. 2014 Jan 1;2(1):3-15.
10. Heaney RP. Defining deficiency of vitamin D. Clinical Laboratory International. 2010 Oct;34:16-9.
11. Hagaman JT, Panos RJ, McCormack FX, Thakar CV, Wikenheiser-Brokamp KA, Shipley RT, Kinder BW. Vitamin D deficiency and reduced lung function in connective tissue-associated interstitial lung diseases. Chest. 2011 Feb 1;139(2):353-60.
12. Elnady HG, EL-Alameey IR, Kamel TB, Youness ER, Kholoussi S. Predictors of reduced serum vitamin D levels among Egyptian children with interstitial lung disease. Journal of The Arab Society for Medical Research. 2014 Jul 1;9(2):67-74.
13. Mulrennan S, Knuiman M, Walsh JP, Hui J, Hunter M, Divitini M, Zhu K, Cooke BR, Musk AW, James A. Vitamin D and respiratory health in the Busselton Healthy Ageing Study. Respirology. 2018 Jun;23(6):576-82.
14. Gilbert CR, Arum SM, Smith CM. Vitamin D deficiency and chronic lung disease. Canadian respiratory journal: journal of the Canadian Thoracic Society. 2009 May;16(3):75.
15. Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DY. Vitamin D levels, lung function, and steroid response in adult asthma. American journal of respiratory and critical care medicine. 2010 Apr 1;181(7):699-704.
16. Monadi M, Heidari B, Asgharpour M, Firouzjahi A, Monadi M, Mirsaied MA. Relationship between serum vitamin D and forced expiratory volume in patients with chronic obstructive pulmonary disease (COPD). Caspian journal of internal medicine. 2012;3(3):451.
17. Foong RE, Shaw NC, Berry LJ, Hart PH, Gorman S, Zosky GR. Vitamin D deficiency causes airway hyperresponsiveness, increases airway smooth muscle mass, and reduces TGF-β expression in the lungs of female BALB/c mice. Physiological reports. 2014 Mar;2(3):e00276.

18. Sluyter JD, Camargo Jr CA, Waayer D, Lawes CM, Toop L, Khaw KT, Scragg R. Effect of monthly, high-dose, long-term vitamin D on lung function: a randomized controlled trial. Nutrients. 2017 Dec 13;9(12):1353.