

How to Cite:

Ahmed, N. B., Abd-Elnaby, E. A., Abd-Elnaiem, S. S., Rabie, W. A., & Ibrahim, R. O. (2022). Vitamin d deficiency and effect of its supplementation on interstitial lung disease (ILD): a randomized clinical trial. *International Journal of Health Sciences*, 6(S7), 818–832.
<https://doi.org/10.53730/ijhs.v6nS7.11313>

Vitamin d deficiency and effect of its supplementation on interstitial lung disease (ILD): a randomized clinical trial

Naglaa Bakry Ahmed*

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

*Corresponding autor, email: naglaa.bakry@kasralainy.edu.eg

Esmat Ali Abd-Elnaby

Professor of chest diseases, Faculty of Medicine, Cairo University, Cairo, Egypt
Email: profesmat1@hotmail.com

Samah Selim Abd-Elnaiem

Assistant professor of Chest diseases, Faculty of Medicine, Cairo University, Cairo, Egypt
Email: samah.selim@ymail.com

Walaa Ahmed Rabie

Assistant professor of Chemical pathology, Faculty of Medicine- Cairo University, cairo, Egypt
Email: wl.rabie@gmail.com

Rania Othman Ibrahim

M.Sc. Chest diseases, Faculty of Medicine, Cairo University, Cairo, Egypt
Email: raniaibraheam81@gmail.com

Abstract---Background: Vitamin D is a steroid hormone that affects the immune system, lung remodeling, and bone health. Aim of the work: to assess serum vitamin D level in non-connective tissue disease-associated interstitial lung diseases (ILD), and to evaluate the impact of vitamin D supplementation. Patients and methods: One hundred and four patients with different types of ILD were randomly assigned to either; Group 1 (intervention): included 52 patients who received vitamin D for 3 months besides their standard treatment, and Group 2 (control): included 52 patients who received only the standard treatment of ILD. Follow up after 3 months. All patients were subjected to; dyspnea scoring, spirometry, six minutes walk test (6-MWT), and measurement of serum vitamin D at the time of enrollment and after 3 months for the intervention group. Results: The mean serum vitamin D level was (8.53 ± 6.29) ng/ml. After 3 months of

supplementation; it significantly increased [5.7 to 18.5 (ng/ml), $p < 0.001$], dyspnea score significantly decreased, significant increase of forced vital capacity (FVC)% and forced expiratory volume in the first second (FEV1)% ($P=0.004$ & 0.02), with improvement of six minute walk distance (6-MWD) and oxygen saturation. The larger the changes in vitamin D, the more the improvement in FVC% and FEV1% [($r=0.41$ & 0.5 ; $p=0.03$ & 0.01)]. Conclusion: Low serum vitamin D level is prevalent among patients with non-connective tissue disease-associated ILD and its supplementation could improve 6-MWD and pulmonary function specifically FVC and FEV1.

Keywords---Interstitial lung diseases, Vitamin D, FVC%, FEV1%, 6-MWT

Introduction

Vitamin D has many non-skeletal biological effects that are important in health and disease in addition to its essential role in calcium homeostasis [1].

There is evidence that supports an association between vitamin D and susceptibility and severity of autoimmune disorders [2]. Clinical studies demonstrated low vitamin D level in connective tissue diseases and its association with diseases activity [3-4]. It may be also involved in the pathogenesis and end-organ dysfunction of these diseases [5].

Interstitial lung diseases (ILD) are increasingly recognized as an important cause of morbidity and early mortality [6]. They are characterized by progressive dyspnea, impairment of gas exchange and both inflammation and fibrosis of the lung parenchyma, with involvement of alveolar, interstitial and vascular spaces [7-8].

Epidemiological studies demonstrated that low serum levels of 25-hydroxy-vitamin D were associated with fibrosis disease in multiple organs [9]. Besides, vitamin D can reduce transforming growth factor-beta1 (TGF- β 1) expression and attenuate TGF- β 1 induced epithelial-mesenchymal transition (EMT) [10-11].

The aim of the study was to assess serum vitamin D level in non-connective tissue disease-associated interstitial lung diseases (ILD), and to evaluate the impact of vitamin D supplementation on the patients' clinical and functional state.

Method

This randomized controlled study was carried out at the Chest Department in collaboration with the Chemical Pathology Department, at Kasr Al-Ainy Hospital, Cairo University during the period from March 2019 to January 2020.

The study was approved by the research ethical committee of the faculty of Medicine, Cairo University (Study number: N-140-2018) and was registered in the

clinical trial registry (NCT: 04100226). An informed written consent was obtained from all patients.

Population of the study:

The study included 104 patients with interstitial lung disease other than connective tissue-associated disease namely; hypersensitivity pneumonitis, sarcoidosis, and idiopathic pulmonary fibrosis who were presented to the Chest Department for accurate assessment and treatment.

They were diagnosed according to the diagnostic algorithm of ILD [12] through multidisciplinary approach involving all the clinical data, laboratory investigations, functional evaluation, high resolution computerized tomography of the chest, and lung biopsy when appropriate.

Exclusion criteria:

- Patients who had other diseases that could contribute to causing vitamin D deficiency (eg. malignancy, chronic renal disease, liver disease, etc.).
- Patients unable to do spirometry or 6-MWT.
- Patients with ischemic heart disease and congestive heart failure.
- Exacerbation of ILD.

Methodology in details:

As shown in figure 1, all enrolled patients were randomly assigned to either:

Group (1) (intervention group): included 52 patients with vitamin D deficient/insufficient who received vitamin D supplementation besides the standard treatment of ILD, or

Group (2) (control group): included 52 patients with vitamin D deficient/insufficient who received only the standard treatment of ILD.

The treatment which was received in the studied population was as the following:

- For both groups: Standard medications of ILD as; corticosteroids, and immune suppressive drugs (Azathioprine, Methotrexate) when appropriate.
- For the intervention group: Vitamin D supplementation in a dose of [200.000 international units of cholecalciferol (vitamin D3)] (Devarol) intramuscular injection every 2 weeks for 3 months for patients with deficient serum vitamin D level (vitamin D level: 0-10 ng/ml), and every month for 3 months for patients with insufficient serum vitamin D level (vitamin D level: 10-30 ng/ml). No vitamin D supplementation for patients with sufficient serum vitamin D level (vitamin D level: 30-100 ng/ml).
- Oral calcium supplementation was supplied in a fixed dose of 600 mg once daily for 3 months for all patients.

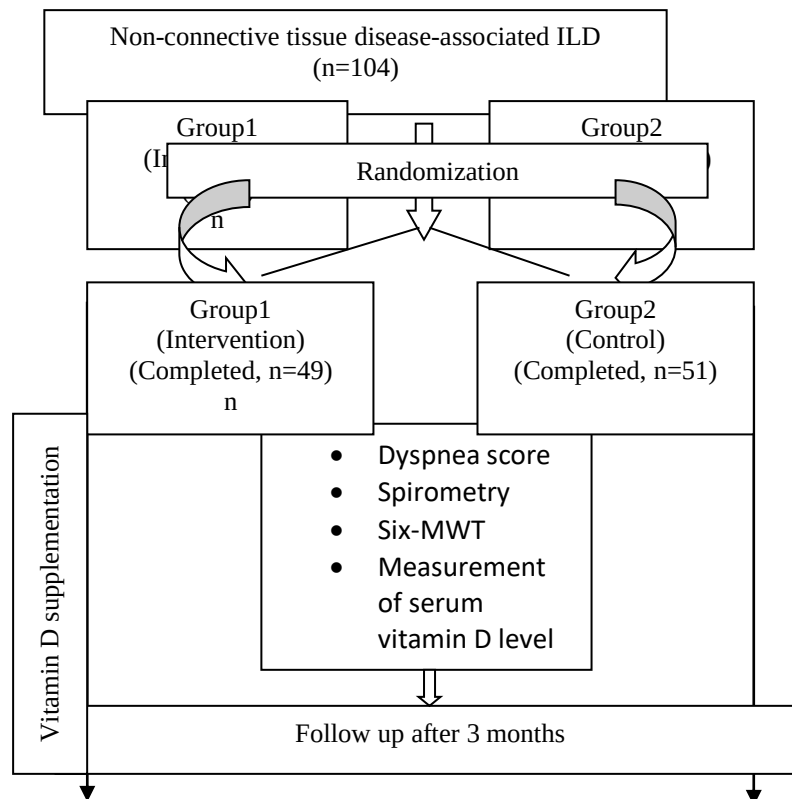


Figure 1: Flow chart represents the study design

All patients were subjected to the following:

- Medical history and physical examination with special concern to personal history including; age, sex, body mass index (BMI), smoking history, drug intake, occupational, and environmental exposure history).
- Determination of dyspnea score:
Dyspnea in daily living was evaluated by the modified medical Research Council (mMRC) scale which consists of five statements that describe almost the entire range of dyspnea from Grade 0 to almost complete incapacity (Grade 4) [13].
- Spirometry:

It was performed By Master Screen Pulmonary Function Test 2012, Care Fusion 234 GmbH, Germany (V-781267-057 version 03.00). According to (Miller et al., 2005) [14], the following parameters were measured and interpreted as percent predicted values; forced vital capacity (FVC%), forced expiratory volume in the 1st second (FEV1%), maximum expiratory flow (MEF 25%), and FEV1/FVC%.

- Six-minute walk test (6-MWT):

Six-minute walk test measures the distance a patient can quickly walk during 6 minutes on a flat, long, hard covered corridor which was 30 meter long, meter by meter marked, and is thought to reflect the patient's functional activity level for daily activities. The 6-MWT was conducted according to the American Thoracic Society guidelines [15]. Reference values for the walked distance are 576 meter for healthy male individuals and 494 meter for healthy female individuals.

Oxygen saturation (SO₂%) was measured before and immediately at the end of 6-MWT using pulse oximetry. The distance walked was calculated. Oxygen desaturation was defined as a fall in oxygen saturation to 88% or less, or a fall of 4% during the 6-MWT [16].

Measurement of serum vitamin D level:

Peripheral venous blood samples were withdrawn using standard venous-puncture technique and then centrifuged. Grossly hemolytic samples were avoided. Specimens were stored up to 48 hours at 2-8 °C or frozen at -20 °C if held for a longer time, prior to assaying.

Serum vitamin D level was measured and its deficiency was determined [17] using solid phase enzyme linked immunosorbent assay (ELISA).

- Follow up after 3 months:

All the patients were followed up for 3 months. Assessment of the dyspnea score and changes of the parameters of spirometry and 6-MWD were carried out besides, measurement of serum vitamin D level after 3 months for the intervention group.

Statistical analysis

Sample size calculation was done using G*Power software version 3.1.2 for MS Windows, Germany. It was done using the comparison of mean distance in 6 minute walk test (6MWT) between cases with interstitial pulmonary fibrosis (IPF) treated with vitamin D supplementation and untreated matched cases, as it was the primary outcome of our study. As reported in previous publication [18], the mean $\pm$ standard deviation (SD) of 6-MWT in untreated group was 392.4 $\pm$ 108meter.

We assumed that vitamin D supplementation will increase the distance by at least 60meter. Accordingly, we calculated that the minimum proper sample size was 52 patients in each arm to be able to reject the null hypothesis with 80% power at α = 0.05 level using Student's t test.

The data were statistically analyzed using Minitab 17.1.0.0 for windows (Minitab Inc., 2013, Pennsylvania, USA). All tests were two sided. A p-value <0.05 was considered significant. Continues data were represented as mean and SD or

median and inter quartile range (IQR), and categorical data were represented as number and %.

Independent t-test or Mann Whitney test used for comparison between two groups of continues data nature, and chi square test for comparison between two or more groups of categorical data.

Paired t-test used to compare between two means before and after intervention. Pearson correlation coefficient used to estimate the linear relationship between two or more numerical variables; the sign before the "r" represent the direction of the relationship.

Results

Patients' characteristics

The study included 104 ILD patients. Their characteristics were shown in table 1. There was no statistical significant difference between the intervention group and the control group as regards to the grade of dyspnea, parameters of spirometry, 6-MWD, resting arterial oxygen saturation, and post 6-MWT oxygen saturation. Low serum vitamin D level was detected and was not significantly different among both groups.

Table (1)
Baseline clinical and functional parameters of the intervention and the control group

Variable	Intervention group (n=52)	Control group (n=52)	P-value
Age (year)	46.2±7.5	48.66±5.4	0.32 ^{\$}
Sex (Female)	41 (78.84%)	41 (78.84%)	1 [#]
BMI (weight/height ²)	29.9±5.85	33.07±7.77	0.07 ^{\$}
Diagnosis			
• HP	24(46.15%)	37 (71.15%)	0.14 [#]
• Sarcoidosis	18 (34.62%)	12 (23.08%)	
• UIP/IPF	10 (19.23%)	3 (5.77%)	
Dyspnea Score	3.031±0.538	2.875±0.609	0.23 ^{\$}
Spirometry			
FVC% predicted	58±22	60±23	0.76 ^{\$}
FEV1% predicted	56±22	58±23	0.7 ^{\$}
FEV1/FVC%	81±16	81±10	0.95 ^{\$}
MEF25% predicted	46±26	45±32	0.89 ^{\$}
Six minute walk test			
6-MWD	259.9±76.1	285.1±82.1	0.2 ^{\$}
Resting SO ₂ %	91±8	93±4	0.14 ^{\$}
Post 6-MWT SO ₂ %	83±12	88±7	0.07 ^{\$}
O ₂ desaturation%	6(3-10)	5(2-7)	0.12 ^{\$\$}
Vitamin D (ng/ml)	5.7(3.6-8.7)	7.2(4.4-15.7)	0.08 ^{\$\$}

BMI: body mass index, HP: hypersensitivity pneumonitis, UIP/IPF: Usual interstitial pneumonia/Idiopathic pulmonary fibrosis, FVC: forced vital capacity, FEV1: forced expiratory volume in the first second, MEF: maximum expiratory flow, 6-MWD:6-minute walk distance, SO₂: oxygen saturation.

Data are represented as mean $\pm$ standard deviation(SD), or median, inter-quartile range (IQR), number (n), percentage (%).

\$: independent t-test, #: Chi square test, \$\$: Mann Whitney test, significant P-value < 0.05.

Effects of vitamin D supplementation

After 3 month of vitamin D supplementation; there was significant improvement of dyspnea (p-value < 0.001).

Both FVC% and FEV1% predicted values were significantly increased, [(p-value=0.004 and 0.02), respectively] while at the level of small airways represented as MEF25%, there was no statistically significant change (p-value=0.3) (table 2, figure 2).

Considering the patients' ability for doing 6-MWT, it significantly improved [(mean $\pm$ SD= 257.30 $\pm$ 74.50 to 299.5 $\pm$ 84.10 meter), p-value < 0.001]. Also, resting oxygen saturation and the percentage of oxygen desaturation (resting oxygen saturation - post 6-MWT oxygen saturation) were significantly improved, (p-value=0.01 and 0.03, respectively).

Table (2)

Statistical analysis of the measured parameters in the intervention group before and after 3 months of vitamin D supplementation

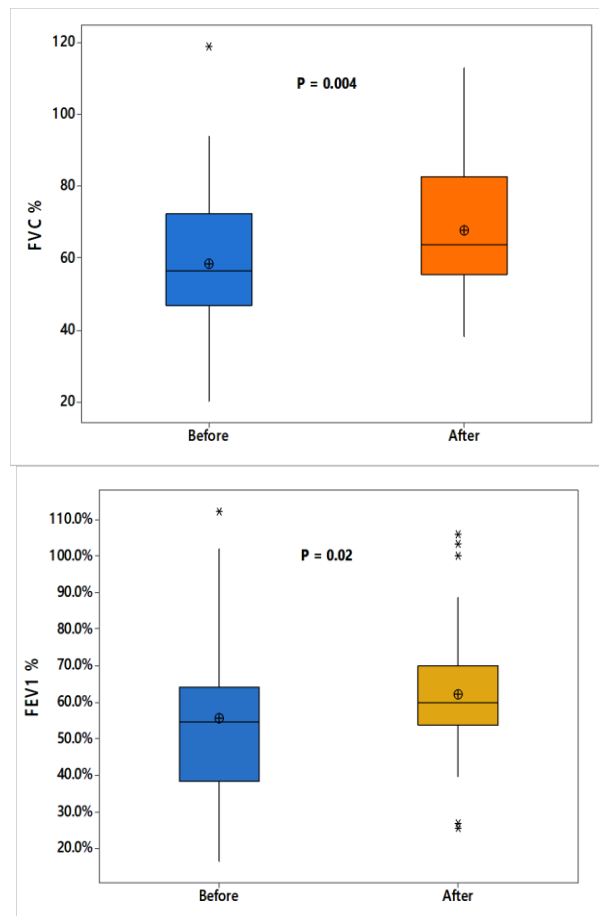
Intervention group Variable	Before vitamin D supplementation (n=49)	After vitamin D supplementation (n=49)	P-value
Dyspnea Score	3.03 $\pm$ 0.54	1.91 $\pm$ 1.00	< 0.001 [^]
FVC% predicted	60 $\pm$ 22	68 $\pm$ 20	0.004 [^]
FEV1% predicted	56 $\pm$ 23	62 $\pm$ 20	0.02 [^]
FEV1/FVC%	80 $\pm$ 16	81 $\pm$ 11	0.70 [^]
MEF25% predicted	41 $\pm$ 23	37 $\pm$ 22	0.30 [^]
6-MWD(meter)	257.30 $\pm$ 74.50	299.50 $\pm$ 84.10	<0.001 [^]
Resting SO ₂ %	91 $\pm$ 8	93 $\pm$ 4	0.01 [^]
O ₂ desaturation %	6 (3-10)	5 (0-7)	0.03 [^]
Vitamin D (ng/ml)	5.7 (3.6-8.7)	18.5 (15-22)	< 0.001 [^]

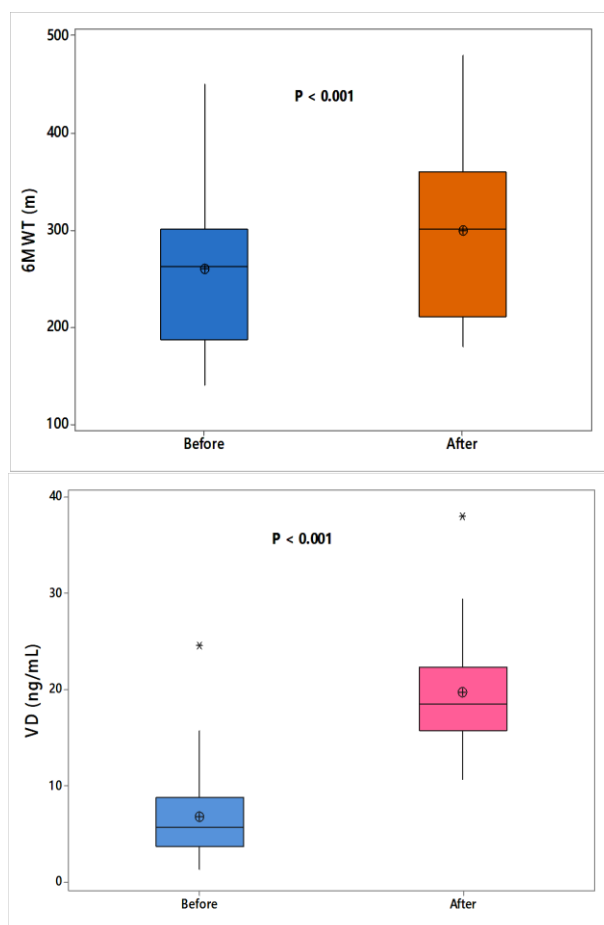
FVC: forced vital capacity, FEV1: forced expiratory volume in the first second, MEF: maximum expiratory flow, 6-MWD:6-minute walk distance, SO₂: oxygen saturation. Data are represented as mean $\pm$ standard deviation(SD), or median, inter-quartile range (IQR).

[^]: Paired t-test, significant P-value < 0.05.

The level of serum vitamin D significantly increased [(5.7 to 18.5 ng/ml), p-value < 0.001] (table 2, figure 2).

Figure2
Significant improvement of the measured parameters in the intervention group after vitamin D supplementation





It worth attention that the larger the changes in vitamin D level after supplementation, the more the improvement in FVC%, FEV1% and MEF25% ($r=0.41, 0.5$ and 0.37 ; p -value = $0.03, 0.01$ and 0.05) respectively (table3). While the changes of the distance in 6-MWT was insignificantly correlated with the changes of vitamin D level (p -value = 0.55).

Table (3)
Correlation between the changes of serum vitamin D level and the changes in the parameters of spirometry and 6-MWD in the intervention group

Variable	Vitamin D level changes	
	r	p-value
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
6-MWD change	0.12	0.55

Person correlation coefficient (r), the sign before r denotes the direction of the relationship, significant P-value < 0.05.

In the control group, the grade of dyspnea was the only parameter that significantly improved after 3 months of follow up (table 4).

Table (4)
Statistical analysis of the measured parameters in the control group before and after 3 months

Control group Variable	Before (n=51)	After 3 months (n=51)	P-value
Dyspnea Score	2.88±0.61	2.13±1.01	< 0.001 [^]
FVC% predicted	61%±23	60±21	0.42 [^]
FEV1% predicted	59±22	59±21	0.84 [^]
FEV1/FVC%	81±11	82±9	0.63 [^]
MEF25% predicted	46±32	46±31	0.86 [^]
6-MWD (meter)	289.5±79.6	291.4±75.7	0.86 [^]
Resting SO ₂ %	93±4	94±3	0.51 [^]
O ₂ desaturation%	5 (2-7)	4 (1-5)	0.59 [^]

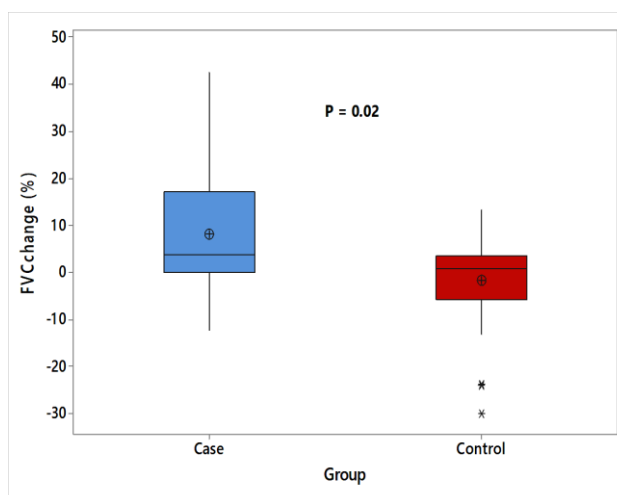
FVC: forced vital capacity, FEV1: forced expiratory volume in the first second, MEF: maximum expiratory flow, 6-MWD:6-minute walk distance, SO₂: oxygen saturation.

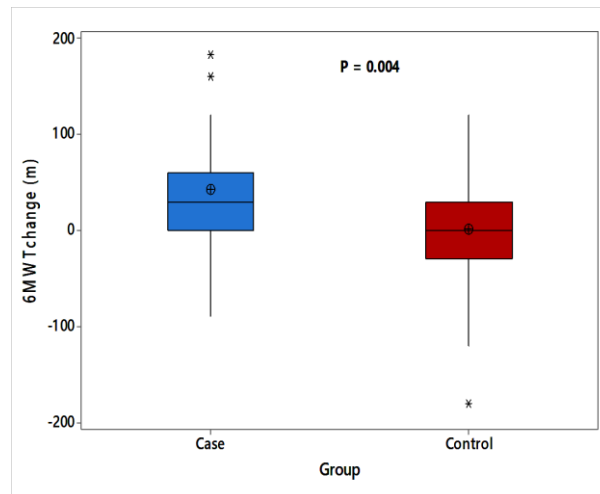
Data are represented as mean ± standard deviation(SD), or median, inter-quartile range (IQR).

[^]: Paired t-test, significant P-value < 0.05.

By comparing the changes of the measured parameters in the intervention group compared to the control group; both the changes of FVC% and 6-MWD were significant high in the intervention group compared to the control group at the end of the 3 months follow up (p-value =0.02 and 0.004) (figure 3).

Figure 3
Significant higher changes of FVC% and 6-MWD among the intervention group compared to the control group





Discussion

The role of vitamin D in the pathogenesis of pulmonary fibrosis and its possible effects through inhibition of TGF- β -induced pro-fibrotic effects in lung fibroblasts and epithelial cells was presented in early experimental studies [19-20]. In addition, Shi et al., 2017 [21] demonstrated that chronic vitamin D deficiency could lead to pulmonary fibrosis through the activation of the renin-angiotensin system (RAS).

The possible beneficial effects of vitamin D supplementation on various clinical and functional outcomes in many respiratory diseases are being of interest and particularly little is known in non-connective tissue related ILD.

The main finding of the study was that patients with different types of ILD (not including connective tissue disease-associated ILD) had low serum vitamin D level and there was a significant improvement of lung function following vitamin D supplementation.

Different studies demonstrated that low serum vitamin D level could affect lung function. Black and Scragg, 2005 [22] showed that lower serum vitamin D were associated with a lower FEV1 in a dose-dependent manner in a general population.

The Third National Health and Nutrition Examination Survey (NHANES III) also supported the finding regarding a connection between a significant relation between vitamin D and pulmonary function tests, specifically FEV1 and FVC [23].

Sutherland and co-workers, 2010 [24] found that vitamin D deficiency impairs lung function; increases airway hyper-responsiveness and can decrease the response to glucocorticoids. In addition to that, Mulrennan and his colleagues, 2018 [25] reported a statistically significant higher level FVC and FEV1 among Caucasian adult population in those with higher vitamin D levels.

The clinical impact of vitamin D on different respiratory diseases is well recognized in the literature as in chronic obstructive pulmonary disease [26-27-28], bronchial asthma [29-30], and pulmonary infections [31].

As regards to ILD, Hagaman and co-workers, 2011 [32] reported that; low vitamin D was highly prevalent in patients with ILD and was associated with the presence of an underlying connective tissue disease and reduced lung function. However, no significant association between lower vitamin D and 6-MWD.

This relation between vitamin D level and lung function comes in agreement with our finding of significant improvement of FVC% (p-value = 0.004) , FEV1% (p-value = 0.02) , and 6-MWD (p-value <0.001) after vitamin D supplementation among the intervention group (table 2). In contrast to our finding, Sluyter et al., 2017 [33] 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.

Furthermore the study demonstrated that patients who received vitamin D supplementation showed significant improvement of both FVC and 6-MWD compared to patients who did not receive vitamin D at the end of follow up period (figure 3).

Conclusion

Vitamin D deficiency is prevalent among patients with non-connective tissue disease-associated ILD and its supplementation could improve the patients' clinical and functional parameters.

List of Abbreviations

Interstitial lung disease (ILD), six minute walk test (6-MWT), forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), six minute walk distance (6-MWD), transforming growth factor-beta1 (TGF- β 1), epithelial-mesenchymal transition (EMT), body mass index (BMI), modified Medical Research Council scale (mMRC), American Thoracic Society (ATS), oxygen saturation (SO₂), maximum expiratory flow (MEF), enzyme linked immunosorbent assay (ELISA), idiopathic pulmonary fibrosis (IPF).

Declarations of interest: none

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

We are thankful to Dr. Mervat Essam, Associate Professor of Internal Medicine, Faculty of Medicine, Cairo University for her help in the study.

References

1. Ali AM., Selim S, Abbassi MM., Sabry NA. Effect of alfacalcidol on the pulmonary function of adult asthmatic patients: A randomized trial. *Ann Allergy Asthma Immunol* 2017; 118(5):557-563.
2. American Association for Respiratory Care (AARC). Clinical practice guideline: exercise test for evaluation of hypoxemia and/or desaturation. *Respir Care*. 2001; 46:514-522.
3. American Thoracic Society Statement ATS. Guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002; 166:111-117.
4. Arns J, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new aetiological and therapeutic considerations. *Ann Rheum Dis*. 2007; 66(9):1137-1142.
5. Black PN and Scragg R. Relationship between serum 25-hydroxyvitamin D and pulmonary function in the Third National Health and Nutrition Examination Survey. *Chest* 2005; 128: 3792-8.
6. Du Bois RM, Albera C, Bradford WZ, Costabel U. 6-minute walk test distance (6MWD) is a reliable, valid, and responsive Outcome measure that predicts mortality in patients with IPF. *Am J Respir Crit Care Med* 2010; 181:A1103
7. Esmat A. Abd Elnaby, Samah S. Abd Elnaiem, Amira I. Mostafa, Dina Sabry, Mohamed K. Haswa. Does vitamin D deficiency worsen the clinical and functional parameters of stable chronic obstructive pulmonary disease patients? *Egypt J Bronchol* 2019; 13:584-590
8. Gilbert CR, Arum SM, Smith CM. Vitamin D deficiency and chronic lung disease. *Can respir J* 2009; 16(3):75-80.
9. Heaney R.P. Defining deficiency of vitamin D. *Clinical Laboratory International*, October 2010, vol. 34: 16-19.
10. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al, Evaluation, Treatment, and Prevention of Vitamin D Deficiency: An Endocrine Society Clinical Practice Guideline, *J Clin Endocrinol Metab* July 2011, 96 (7): 1911-1930.
11. Jiang F, Yang Y, Xue L, Li B and Zhang Z, 1-25-dihydroxyvitamin D3 Attenuates TGF-Induced Pro-Fibrotic Effects in Human Lung Epithelial Cells through Inhibition of Epithelial-Mesenchymal Transition. *Journal Nutrients* Sept. 2017; 9(8) : 1-3.
12. Johansson KA, Hambly N, Assayag D & Ryerson KJ. Update in the diagnostic approach to fibrotic interstitial lung disease, *Canadian Journal of Respiratory, Critical Care and Sleep Medicine* 2019; 10 :1-6.
13. Kabel AM, Abd Elmaaboud MA, Atef A, Baali MH. Ameliorative potential of linagliptin and/or calcipotriol on bleomycin-induced lung fibrosis: In vivo and in vitro study. *Environ. Toxicol. Pharmacol.* 2017, 50, 216-226.
14. Kamen DL, Aranow C. Vitamin D in systemic lupus erythematosus. *Curr Opin Rheumatol*. 2008; 20 (5): 532-537.

15. Kamen DL, Cooper GS, Bouali H, Shaftman SR, Hollis BW, Gilkeson GS, et al., Vitamin D deficiency in systemic lupus erythematosus. *AutoimmunRev.*2006 ; 5(2):114–117.
16. Liu J, Dong YQ, Yin J, Yao J, Shen J, Sheng GJ, et al.,. Meta-analysis of vitamin D and lungfunction in patients with asthma. *Respiratory Research* 2019; 20(1):161
17. Martineau AR, Jolliffe DA, Hooper RL Greenberg, L, Aloia JF, Bergman P., et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ* 2017; 356:i6583. <http://dx.doi.org/10.1136/bmj.i6583>
18. Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med.* 2005; 142: 963–967.
19. Mehrad and Strieter. Fibrocytes and the Pathogenesis of Diffuse Parenchymal Lung Disease. *Fibrogenesis& Tissue Repair*; 2012; 5 Suppl 1: S22.
20. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A et al., ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J* 2005; 26:319–338.
21. Monadi M, Heidari B, Asgharpour M, Firouzjahi A, Monadi M, Ghazi Mirsaied MA et al.Relationship between serum Vitamin D and forced expiratory volume in patients with chronic obstructive pulmonary disease (COPD) *Caspian J Intern Med.* 2012;3:451–455.
22. MouyisM, Ostor AJ, Crisp AJ. Hypovitaminosis D among rheumatology outpatients in clinical practice. *Rheumatology (Oxford)* 2008 ; 47(9):1348–1351.
23. Mulrennan S, Knuiman M, Walsh Jp, Hui J, Hunter M , Divitini M et al.Vitamin D and respiratory health in the Busselton Healthy Ageing Study, official journal of the Asian Pacific Society of Respirology Jess Reid, University of Western Australia 2018; 132-139.
24. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, Watanabe F, Arizono S: A simple assessment of dyspnea as a prognostic indicator in idiopathic pulmonary fibrosis. *Eur Respir J* 2010, 36:1067–1072
25. Ramirez AM, Wongtrakool C, Welch T, Steinmeyer A, Zugel U, Roman J et al.,Vitamin D inhibition of pro-fibrotic effects of transforming growth factor beta1 in lung fibroblasts and epithelial cells. *J.SteroidBiochem. Mol. Biol.* 2010, 118, 142–150.
26. Saha K. Interstitial lung disease: Diagnostic approach. *J Assoc Chest Physicians.* 2014; 2:3-15.
27. Shi Y, LiuT, Yao L, Xing Y, Zhao X, Fu J. et al, Chronic vitamin D deficiency induces lung fibrosis through activation of the renin-angiotensin system. *Am J physiol Cell physiol.* June, 2017; 1-10.
28. Sluyter JD, Camargo CA, Waayer JD, Lawes CM, Toop L, Khaw KT et al.Effect of Monthly, and High-Dose, Long Term Vitamin D on Lung Function: A Randomized Controlled Trial *Nutrients* 2017, 9, 1353.
29. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2022). Post-pandemic health and its sustainability: Educational situation. *International Journal of Health Sciences*, 6(1), i-v. <https://doi.org/10.53730/ijhs.v6n1.5949>
30. Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DY. Vitamin D levels, lung function, and steroid response in adult asthma. *Am J Respir Crit Care Med.* 2010; 181: 699–704.

31. Tzilas V, Bouros E, Barbayianni I, Karampitsakos T, Kourtidous S, Ntassiou M, et al. Vitamin D prevents experimental lung fibrosis and predicts survival in patients with idiopathic pulmonary fibrosis. *Pulmonary Pharmacology & Therapeutics*. 2019, 55, 17–24.
32. Zhang Z, Yu X, Fang X, Liang A, Yu Z, Gu P. et al. Preventive effects of vitamin D treatment on bleomycin-induced pulmonary fibrosis. *Sci. Rep.* 2015, 5, 17638.
33. Zhu M, Wang T, Wang C, Ji Y. The association between vitamin D and COPD risk, severity, and exacerbation: an updated systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2016; 11(1):2597–2607.