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Original Article

Mechanism of High Dosage Vitamin D Supplementation on The Lung Function and Quality of Life of Stable COPD Patients

Adyan Donastin[1], Muhammad Amin[2,*], Yulistiani[3]

ABSTRACT

Background: Oxidative stress results from the amplification mechanism of COPD, which leads to decreased lung function and the quality of life of the sufferers. Vitamin D has a function in reducing oxidative stress levels through several mechanisms, which can be revealed by analyzing several biomarkers to determine the role of vitamin D on lung function and the quality of life of stable COPD patients. **Methods:** The subjects included GOLD 2 and 3 stable COPD patients who had 25(OH)D levels of < 32 ng/ml and were receiving bronchodilator Indacaterol maleate therapy. The biomarkers examined included Nrf2, HDAC2, MDA, MMP-9, pulmonary function tests 6MWT, and QOL. The patients in the control and treatment groups were administered with vitamin D at a dose of 1,000 and 5,000 IU, respectively, for three months. **Results:** The administration of vitamin D to the patients in the control and treatment groups can significantly reduce oxidative stress, as evidenced by reduced MDA (p-value < 0.01) and MMP-9 levels (p-value < 0.01). Vitamin D affects exercise tolerance, as evidenced by 6MWT (p-value = 0.01). Vitamin D affects the quality of life, as evidenced by 6MWT (p-value = 0.01). Vitamin D affects Nrf2 levels (p-value = 0.08) and HDAC2 (p-value = 0.01). **Conclusion:** The pathway analysis through the study of the Nrf2, HDAC2, MMP-9, and MDA levels does not prove that vitamin D can prevent decreased lung function and quality of life in patients with stable COPD.

Key words: Oxidative Stress, COPD, Vitamin D, Nrf2, HDAC2, MDA, MMP-9, FEV_1, FVC, FEF_{25-75}, 6MWT, QOL.

Adyan Donastin[1], Muhammad Amin[2,*], Yulistiani[3]

[1]Doctoral-Level Medical Science Study Program, Faculty of Medicine, Airlangga University, Surabaya, INDONESIA; Faculty of Medicine, Nahdhatul Ulama Surabaya University, Surabaya, INDONESIA.

[2]Pulmonology and Respiratory Medicine, Faculty of Medicine, Airlangga University, Surabaya, INDONESIA.

[3]Faculty of Pharmacy, Airlangga University, Surabaya, INDONESIA.

Correspondence

Muhammad Amin

Pulmonology and Respiratory Medicine, Faculty of Medicine, Airlangga University, Surabaya, INDONESIA.

E-mail: amin.fkua@gmail.com

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a common preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation in the airways and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases and influenced by host factors, including abnormal lung development. Significant comorbidities can have a significant impact on morbidity and mortality. COPD is a global health problem of the 21st century. More than three million people died from COPD in 2012, accounting for 6% of all deaths globally.[1,2] The 2018 Basic Health Research (Riskesdas) found that the prevalence of COPD in Indonesia reached 4.5%. It significantly correlated to the incidence of oxidative stress.[1,3-5]

Oxidative stress is the result of the amplification mechanism of COPD. The elevated oxidative stress cases possibly resulted from decreased endogenous antioxidants in COPD patients due to decreased levels of Nuclear factor-erythroid-2 related factor 2 (Nrf2), which regulates many antioxidant genes.[1,6,7] Nrf2 regulates the expression of several oxidant signaling proteins to affect a number of programmed cellular functions.[8,9] This transcription factor is a major sensor of oxidative stress in cells. Under conditions of high levels of oxidative stress, such as COPD, the activity of Nrf-2 decreases due to the downregulation of HDAC2, which causes Nrf-2 to become unstable.[10]

Histone deacetylase 2 (HDAC2) plays an important role in suppressing inflammatory gene expression by preventing histone acetylation. HDAC2 activation in the alveoli macrophages of smokers is less than that in the alveoli macrophages of non-smokers. HDAC2 levels tend to decrease in patients with chronic diseases such as COPD. A decrease in HDAC2 levels is associated with increased steroid resistance and the expression of proinflammatory genes, one of which is MMP-9.[11,12] Matrix metalloproteinases-9 (MMP-9) play an important role in the development of emphysema in COPD. An imbalanced MMP-9 and Tissue Inhibitors of Metalloproteinases (TIMP) level is considered a factor that influences the pathogenesis of COPD, which causes a progressive decline in lung function. Proper management of patients with COPD to prevent continuous amplification is the objective of improving the patients' lung function. In this case, the researchers used high doses of vitamin D given every day for three months.[13-16]

Vitamin D plays a crucial role in reducing oxidative stress levels. Vitamin D enters the nucleus and binds to the retinoid X receptor (RXR), and then binds to the vitamin D response element (VDRE) located on a large number of genes, which can activate the expression of many antioxidant genes, including Nrf2, g-glutamyl transpeptidase (g-GT), glutamate-cysteine ligase (GCLC), glutathione reductase (GR), and glutathione peroxidase (Gpx).[17-19] Vitamin D is also a powerful antioxidant that facilitates the balance of mitochondrial activity, preventing protein oxidation associated with oxidative stress, lipid peroxidation, and DNA damage. The active form of vitamin D, 1.25(OH)2D3, can reduce the inflammatory response of the airways and the levels of inflammatory cytokines in Bronchoalveolar Lavage (BAL). This active form can inhibit cell proliferation during hypoxia.[20-23]

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According to the aforementioned background, this study aims to determine the mechanism of vitamin D supplementation at a dose of 5,000 IU administered in three months to prevent decreased lung function and quality of life of patients with stable COPD.

METHODS

This study is an experimental study involving two treatment groups with a total sample of six patients for each treatment group, totaling twelve patients. The samples include COPD patients treated at the Jemursari Islamic Hospital, Surabaya, where this study was conducted for three months. The sampling was conducted using the random sampling technique in COPD patients who met the inclusion and exclusion criteria. The inclusion criteria included patients diagnosed with GOLD 2 and GOLD 3 grade COPD, patients with COPD who were routinely treated and received standard bronchodilator therapy, patients who were willing to sign an informed consent form, patients with 25(OH)D levels lower than 32 ng/ml, male patients aged 40-80 years, and patients with normal liver and kidney function. Meanwhile, the exclusion criteria included patients with shortness of breath other than COPD and having an allergy to vitamin D. The samples were declared dropped out if they moved to a new residence, could not be contacted, died, and did not take vitamin D for two consecutive weeks. Ethical clearance for this study has been issued by the Jemursari Islamic Hospital, Surabaya, based on a certificate of ethical clearance No. 014/ KEPK-RSISJS/ III/ 2022.

The samples were divided into two groups, namely the control group (K) and the treatment group (P), each consisting of 6 samples. Samples in the control group were given 1,000 IU vitamin D supplementation, while samples in the treatment group were given 5,000 IU vitamin D supplementation with standard therapy given to all groups. An examination was carried out using the Enzyme-Linked Immunosorbent Assay (ELISA) measurement reagent from BT LAB (Bioassay Technology Laboratory) for levels of HDAC2 (Cat No E0988 Hu), levels of Nrf2 (Cat No E3244 Hu), levels of MDA (Cat No E0017Ge), levels of MMP-9 (Cat No E0936 Hu), vitamin D levels (Cat No E1981 Hu), and lung function in both sample groups. All measurements were made after the reaction was terminated by the addition of an acid-stopping solution, and the absorbance was measured at 450 nm. Lung function examinations were performed, including VC (Vital Capacity), FVC (Forced Vital Capacity), FEV_1 (Forced Expiratory Volume in One Second), FEF_{25-75} (mean flow rate in the middle of the forced expiratory volume), and 6MWT (Six- minute walk test) to measure exercise tolerance, as well as the SGRQ (St. George Respiratory Questionnaire) to measure the quality of life in COPD sufferers. All of the above examinations were performed before and after the vitamin D therapy treatment.

Data analysis

The data obtained were then analyzed statistically using the SPSS program. A Statistical test using the Shapiro–Wilk test to determine the normality of the data and a homogeneity test of the data using the Lavene test were carried out. When the data was normal and homogeneous, the MANOVA test would be conducted. Otherwise, data transformation would be performed and proceeded to the MANOVA test. The path analysis test was then performed to prove the mechanism.

RESULTS

During the study, one patient in the control group and one patient in the treatment groups were declared dropped out due to not taking vitamin D for more than two weeks consecutively.

Identification of the patients' characteristics based on Table 5.1 shows that all patients in both the control and treatments group were male (100.00%). The patients in the control group had an average age of 61.00 ± 3.39 years. The patients in the treatment group had an average age of 62.80 ± 4.82 years. The results of the difference test in the control and treatment groups revealed no differences in all the characteristics of the respondents.

Vitamin D administration in the control group had no side effects on liver function (p-value = 0.50) and kidney function (p-value = 0.89). Vitamin D administration in the treatment group had no side effects on liver function (p-value = 0.14) and kidney function (p-value = 0.89).

The results of the Manova test indicated no difference in the levels of Nrf2 (p-value = 0.08), FEV1 (p-value = 0.94), FVC (p-value = 0.74), FEF 25-75 (p-value = 0.51), and QOL (p-value = 0.06) before and after the administration of vitamin D. The results of the analysis indicated differences in the levels of MMP9 (p-value < 0.01), MDA (p-value < 0.01), HDAC2 (p-value < 0.01), and 6MWT (p-value < 0.01) before and after the administration of vitamin D.

Then a t-test is performed in linear regression on all indicators, the results of which are presented in the path analysis image in Figure 1.

DISCUSSION

The results of this study prove that vitamin D activates the transcription Nrf2 by decreasing the level of oxidative stress characterized by a significant decrease in the MDA levels of patients in the treatment and control groups. It is consistent with the results of previous studies regarding the role of vitamin D in reducing oxidative stress.[24,25] New findings in this study prove that vitamin D administered at a dose of 5,000 IU, even at a lower dose of 1,000 IU, for a relatively short time of three months can significantly reduce oxidative stress without being followed by an increase in Nrf2 levels. The role of vitamin D as an antioxidant through the regulation of Nrf2 transcription mediated by the VDR (vitamin D receptor) is very effective because this transcriptional regulation requires relatively low levels of Nrf2 but can significantly reduce the level of oxidative stress.[26]

Based on the analysis results, administering vitamin D at a dose of 5,000 IU results in differences in HDAC2 levels before and after the administration. It is consistent with the results of previous studies that vitamin D induces the expression of HDAC2.[27,28] However, it differs from the results of Huang's study, proving that 1.25(OH)2D3 reduced HDAC2 expression.[29,30] An increase in HDAC2 levels in high-dose vitamin D supplementation for three months is expected to reduce the amplification of the inflammatory response and increase sensitivity to corticosteroids in COPD patients.

The analysis results reveal differences in MDA levels before and after the administration of vitamin D at a dose of 1,000 IU and 5,000 IU. It is similar to several studies that found that vitamin D supplementation could reduce MDA levels.[31-34] The results of this study prove that vitamin D supplementation at a dose of 5,000 IU, even at a lower dose of 1,000 IU for three months, can significantly reduce MDA levels.

The analysis results reveal differences in MMP9 levels before and after the administration of vitamin D at a dose of 1,000 IU and 5,000 IU. It is similar to previous studies that prove that there is a correlation between vitamin D supplementation and reduced levels of MMP-9.[35-37]

The results of the pathway analysis through the study of the Nrf2, HDAC2, MMP-9, and MDA levels (Figure 1) do not prove that vitamin D can prevent decreased lung function and quality of life in patients with stable COPD. However, the results of the path analysis indicate a correlation between MMP-9 and FVC levels with HDAC2 levels. It is in line with Yan Jiang's study that HDAC2 has an important role in COPD pathogenesis.[38] The results of previous studies prove that HDAC2 expression can reduce MMP-9.[39,40] It is similar to the results of Maranatha's study that there is a correlation between MMP-9 and restrictive lung disease conditions in cases of pulmonary TB.[41]

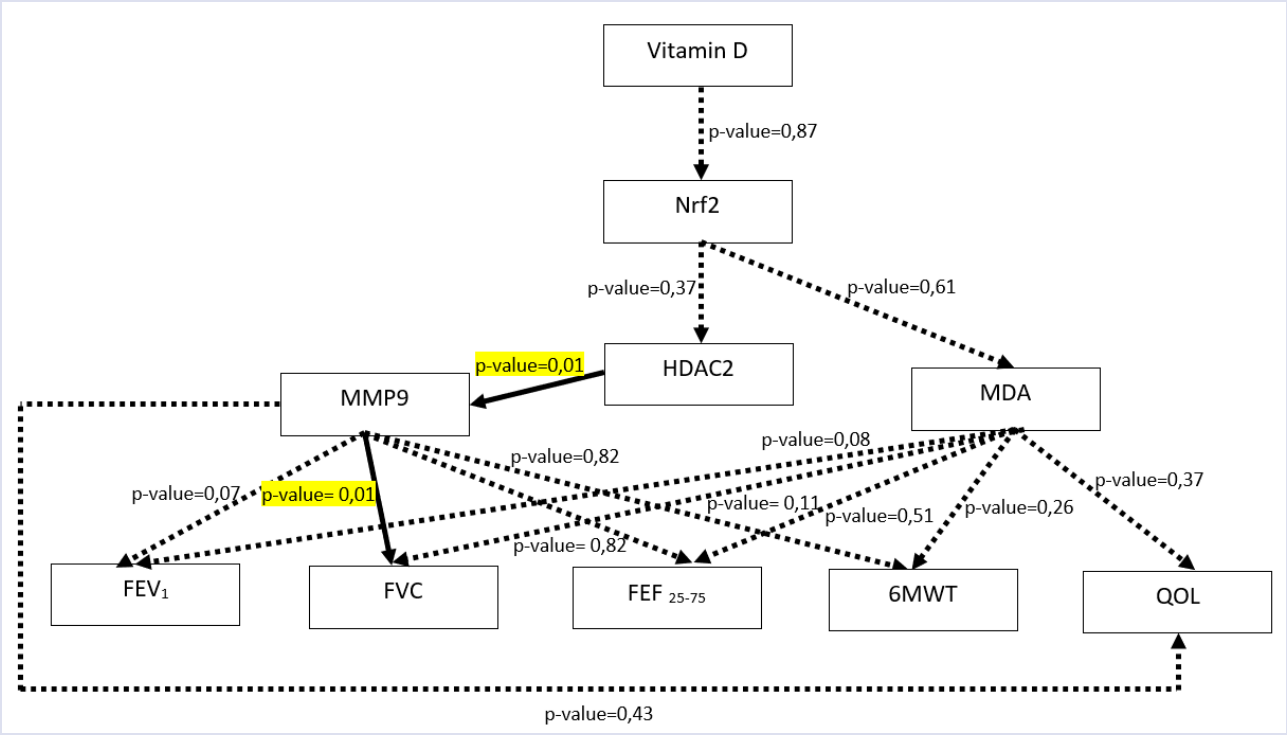

Figure 1: **Path identification**

Table 1: **Patients' characteristics.**

Characteristic	Control group		Treatment group		p-value
	n	%	n	%	
Sex (male)	5	100.00	5	100.00	0.42
Characteristic	**Mean**	**SD**	**Mean**	**SD**	**p-value**
Age (years)	61.00	3.39	62.80	4.82	0.42
VC (% pred)	70.20	19.63	59.40	9.24	0.31
FVC (% pred)	69.20	20.78	55.00	20.94	0.42
FEV_1 (% pred)	52.00	13.66	40.00	5.43	0.10
$FEF_{25-75\%}$ (%)	23.00	9.92	24.40	7.89	1.00
QOL	43.44	17.10	54.43	15.24	0.42
Symptom	62.38	17.31	66.10	16.86	1.00
Activity	47.79	10.20	67.19	21.68	0.22
Impact	34.36	27.35	48.08	22.52	0.55
SGPT pre	21.60	6.73	13.40	6.35	0.10
SC pre	1.19	0.46	1.02	0.16	0.55
6 MWT	214.88	72.42	198.40	53.77	0.69
Vitamin D	8.64	4.85	7.63	2.73	0.84
HDAC2	1.70	0.66	1.50	1.03	0.84
Nrf2	11.24	2.81	10.39	2.42	0.69
MDA	5.05	1.31	4.89	1.50	1.00
MMP9	1,298.14	212.30	1227.42	318.91	0.69
SGPT post	15.60	8.73	11.60	5.50	0.22
SC post	0.91	0.51	1.03	0.12	0.55

Table 2: **A test of effect of vitamin D administration on liver and kidney functions.**

Group	Variable	Before		After		p-value
		Mean	SD	Mean	SD	
Control	SGPT	21.60	6.73	15.60	8.73	0.50
	SC	1.19	0.46	0.91	0.51	0.89
Treatment	SGPT	13.40	6.35	11.60	5.50	0.14
	SC	1.02	0.16	1.03	0.12	0.89

The results of this study do not prove the expected hypothesis. Previous studies prove that vitamin D plays a role in improving lung function and improving quality of life but with a longer study time than that of this study.[42-44] Nonetheless, this study succeeds in revealing the benefits of administering vitamin D at a high dose of 5,000 IU for just three months in reducing oxidative stress levels, as evidenced by the significant reduction in MDA and MMP-9 levels. It will be very beneficial in the management of COPD to prevent the progression of the disease.

The role of vitamin D supplementation has been shown to not correlate with Nrf2 and HDAC2, which can be explained by the mechanism of action of Nrf2 on cells. In basal conditions, Nrf2 is in the cytoplasm, but under oxidative stress conditions, the interaction of Nrf2-Keap1 (Kelch-like-ECH-associated protein 1) is disturbed according to the dose received. It leads to the translocation of Nrf2 to the nucleus, where Nrf2 activates the transcription of antioxidant genes and detoxification by binding to antioxidant response elements (AREs) in their regulatory region.[45,46] This study proves that there is a significant decrease in MDA and MMP9 levels as parameters of oxidative stress, which causes Nrf2 to continue to be degraded in a Keap1-dependent manner through the proteasome pathway. The process of antioxidant transcription initially occurred due to an oxidative stress process, so the Nrf2 levels should be low. After a while, when the oxidative stress process declined, this reaction did not occur, so the Nrf2 level increased. However, such changes in this study were insignificant, possibly due to the samples used being patients with stable grade 2 and 3 COPD.

CONCLUSION

It is not proven that high doses of vitamin D administered in a short time can prevent a decrease in lung function and quality of life in patients with stable COPD through the study of their Nrf2, HDAC2, MMP-9, and MDA levels. However, the results of the path analysis indicate a correlation between HDAC2 levels and MMP-9 levels (p-value = 0.01), as well as between MMP-9 levels and FVC levels (p-value = 0.01). Vitamin D supplementation at a dose of 5,000 IU, even at a lower dose of 1,000 IU for three months, can significantly reduce MDA levels.

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CONFLICTS OF INTEREST

There are no conflicts of interest in this study report as it was privately funded by the researcher in order to complete his doctoral program.

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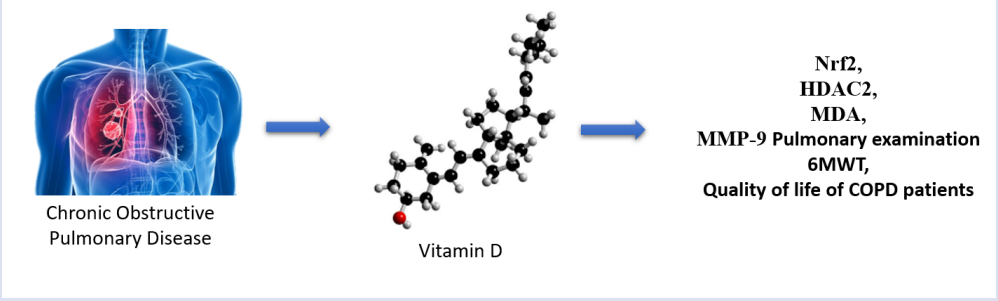
GRAPHICAL ABSTRACT



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