



The Effect of Vitamin-D Supplementation on HDAC2 Levels in Stable COPD Patients

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ARTICLE INFORMATION

Received: March 27, 2025

Revised: July 17, 2026

Available online: August 2026

KEYWORDS

Chronic Obstructive Pulmonary Disease; Vitamin D; HDAC2

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of global mortality, with persistent lung inflammation contributing to its progression. This inflammation is partially due to reduced levels of the Histone deacetylase 2 (HDAC2) protein. Research shows that Vitamin D can modulate HDAC2 levels and slow the advancement of COPD. This experimental study aimed to evaluate the effect of vitamin D supplementation on HDAC2 expression in stable COPD patients at Jemursari Islamic Hospital. Five randomly selected COPD patients received a daily dosage of 5000 IU of Vitamin D for three months. Serum levels of 25(OH) D and HDAC2 were measured before and after the intervention. The results showed a significant increase in both Vitamin D and HDAC2 levels, with a notable, though not statistically significant, improvement in lung function. The findings suggest that consistent Vitamin D supplementation can reduce inflammation by raising HDAC2 levels, potentially slowing lung damage in COPD patients. Therefore, Vitamin D treatment is beneficial in managing COPD by improving lung health and preventing disease progression.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a chronic progressive lung medical condition characterised by respiratory problems and chronic airflow blockage, often resulting from exposure to toxic chemicals, notably cigarettes. Chronic Obstructive Pulmonary Disease (COPD) is globally recognised as a leading cause of high mortality rates. This condition ranks as the third leading cause of death globally and has a prevalence of over 80% in nations with poor to moderate incomes. Within Indonesia, the estimated risk level is at 9.2 million individuals (Jarhyan et al., 2022). Chronic obstructive pulmonary disease (COPD) involves persistent inflammation of the lungs, leading to a decline in quality of life by disrupting daily activities. Chronic obstructive pulmonary disease (COPD) patients see incomplete recovery due to persistent inflammation resulting from the release of pro-inflammatory cytokines and chemokines. This inflammation can lead to tissue damage and obstruction of airflow in the lungs (Global Initiative for Chronic Obstructive Lung Disease, 2022). According to estimates, up to 85% of individuals with COPD are smokers due to the substantial reduction in lung function caused by exposure to tobacco smoke. Several specific medications, including Theophylline, beta2-agonists (LABA), and inhaled corticosteroids, are beneficial in treating this condition. Nevertheless, the incidence of COPD cases continues to rise swiftly (Li et al., 2020).

Histone deacetylase 2 (HDAC2) is an enzyme essential for gene regulation in the process of chromatin remodelling. Individuals with COPD experience a reduction in HDAC2 gene expression, leading to elevated histone acetylation and the production of pro-inflammatory genes. The immunomodulatory action of vitamin D involves its binding to receptors, including macrophages, B cells, and T cells, therefore enhancing the immune response through the reduction of inflammation. At present, vitamin D is utilised as a medication that has a significant impact on cases of COPD due to its ability to influence associated systemic effects and its gene regulatory activities that are believed to provide protection against lung illness. Most of the synthesis of vitamin D occurs from pre-vitamin D3 in the skin of humans. By means of solar radiation, it will undergo synthesis from 7-dehydrocholesterol. Furthermore, fish liver oil, fish fat, liver, egg yolks, and cheese were identified as sources of vitamin D (Li et al., 2020).

According to Sultana et al., (2022), the presence of vitamin D inhibits the growth of Th 1 and Th17 cells, which play a role in inflammation. Consequently, insufficient levels of vitamin D can exacerbate symptoms by reducing lung function and increasing the frequency of lung exacerbations. The primary role of this vitamin is to facilitate bone metabolism. Furthermore, it has the ability to decrease the synthesis of inflammatory cytokines (IL-5, IL-9, and IL-13) in type-9 T-helper cells and so act as producers of the immune system. Nevertheless, this can be impaired if the patient suffers from a lack of vitamin D, which has implications for lung function, inflammation, and the prognosis of associated disorders (Li et al., 2020). Furthermore, there is a correlation between vitamin D insufficiency and chronic illnesses, including autoimmune disorders, cardiovascular disorders, and cancer (Janssens et al., 2012). Vitamin D, when used in long-term treatment and at the correct dosage, can effectively prevent acute exacerbations in individuals with COPD. Prolonged exposure to cigarette smoke as a catalyst for COPD will activate intracellular pathways (NF- κ B and MAPK p38) that are responsible for initiating inflammation. Furthermore, these results suggest that vitamin D may provide protection against inflammation and injury to lung tissue by blocking intracellular signaling pathways and stimulating profibrotic mediators (Khan et al., 2017).

Prior research has demonstrated that vitamin D exerts a therapeutic impact by regulating HDAC2 levels in individuals with chronic obstructive pulmonary disease (COPD). In order to decrease inflammation and enhance responsiveness to corticosteroids, vitamin D has the ability to enhance the activity of HDAC2. According to Janssens W et al. (2012), augmenting HDAC2 levels can mitigate oxidative damage caused by vitamin D supplementation. Additional research indicates a correlation between insufficient levels of vitamin D and pulmonary function, elucidated by variations in lung volume. This correlation can be linked to the association between chronic obstructive pulmonary disease (COPD) and the vitamin D status inside the body. (Nur Aini et al., 2023). Furthermore, a similar study elucidated that the rising occurrence of vitamin D insufficiency among patients with chronic obstructive pulmonary disease (COPD) will lead to a decline in their quality of life. Therefore, the administration of Dini vitamins as a medication can

effectively lower the occurrence of exacerbations. Nevertheless, there is currently no robust evidence indicating that this supplementation can effectively mitigate harm to the pulmonary organs (Mullin & Milne, 2023). The efficacy of vitamin D supplementation in managing COPD has been extensively established, however numerous studies have failed to yield consistent findings. Therefore, we undertook a study specifically targeting COPD patients. The objective of this study is to assess the efficacy of vitamin D supplementation in improving lung function in patients with chronic obstructive pulmonary disease (COPD).

METHOD

Research Design

This research is a true experimental study using a pre-test and post-test method. The levels of HDAC2 were measured pre and post-supplementation of vitamin D given for 3 months. This research will be conducted at the Pulmonary Clinic of Islamic Hospital Jemursari Surabaya. The research will take place from April 2024 to June 2024. The sample in this study consists of some COPD patients who meet the inclusion and exclusion criteria as follows: Inclusion criteria: a. Diagnosed with COPD stage GOLD 2 and GOLD 3, b. COPD patients who regularly seek treatment and receive standard bronchodilator therapy, c. Willing to sign informed consent, d. Patients with 25(OH)D levels < 32 ng/ml, e. Male gender aged 40-80 years, f. Normal liver function, g. Normal kidney function. Exclusion criteria: a. Suffering from respiratory diseases other than COPD, b. Allergy to vitamin D. Drop-out criteria: a. Moving to an address that cannot be contacted, b. Passing away, c. Not taking vitamin D for two consecutive weeks.

Vitamin D Delivery

This vitamin exists in two active forms: vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol). Calcitriol, also known as 1,25-(OH)₂D₃, is a pleiotropic hormone that emerges as the active form of vitamin D following its conversion by the kidneys from calcidiol, which is excreted by the liver. This conversion process is facilitated by the enzyme cytochrome P450 hydroxylase 1- α . Salivary 25(OH)D indicates the level of vitamin D. Patient administration of vitamin D consists of Cholecalciferol at a dosage of 5000 IU. Patients who are chosen will thereafter be administered vitamin D at a dosage of 5000 IU for a duration of 3 months. Monthly monitoring of adherence and regular intake of vitamin D will be conducted. Upon completion of the study period, the patient's blood will be collected for the purpose of assessing Vitamin D levels and conducting other test.

Pulmonary Function Test

Assessments of pulmonary function are performed weekly using a calibrated spirometer to measure volume and flow. The mouthpiece and nose clip are intended for one-time usage only. Conditions of the patients: The patient should abstain from smoking for a minimum of 2 hours before the examination, avoid

excessive eating immediately before the examination, avoid wearing too tight clothing, use short-acting bronchodilators at least 8 hours before the examination, and use long-acting bronchodilators at least 24 hours before. The testing protocol involves measuring height and calculating the expected values using the standard lung function statistics from the Pneumobile Project Indonesia. The examination is conducted while standing, evaluating VC, FVC, FEV1, and FEF25-75 ratios.

VitD level Examination

The Vitamin D ELISA kit was purchased from BT LAB (Bioassay Technology Laboratory, Cat. No E1981 Hu). This kit operates based on the principle of Enzyme-Linked Immunosorbent Assay (ELISA). Previous to use, the plate has been coated with antibodies targeting human CYP27B1. The CYP27B1 enzyme found in the sample is introduced and forms complexes with the antibodies presented on the plate. Following that, biotinylated human CYP27B1 antibodies are introduced and selectively attach to the CYP27B1 present in the sample. Next, streptavidin-HRP is introduced and forms a complex with the biotinylated CYP27B1 antibodies. Following incubation, any unbound Streptavidin-HRP is removed by washing during the washing process. A substrate solution is subsequently introduced, and the coloration follows a proportional relationship with the quantity of human CYP27B1. The addition of an acidic stop solution terminates the process, and absorbance is measured at 450 nm.

HDAC2 Examination

An ELISA kit for the HDAC2 enzyme was acquired from BT LAB (Bioassay Technology Laboratory, Cat No E0988 Hu). The plate has been previously coated with human HDAC2 antibodies. HDAC2 in the sample that was added binds to the antibodies that were coated on the wells. Next, biotinylated human HDAC2 antibodies are added and find HDAC2 in the sample. Subsequently, streptavidin-HRP is added and binds to the biotinylated HDAC2 antibodies. During the washing step, the unbound Streptavidin-HRP is washed after incubation. The substrate solution is then added, and the colour develops in proportion to the amount of human HDAC2. The reaction was terminated by adding an acid-stop solution, and the absorbance was measured at 450 nm.

RESULT

Supplementing with 5000 IU of Vitamin D substantially boosts vitamin D levels during a span of 3 months.

The empirical findings suggest that the administration of vitamin D at a dosage of 5000 IU over a period of 3 months can substantially enhance vitamin D levels in comparison to the levels before the supplementation (pre vs post, 7.63 ± 2.73 vs 14.26 ± 2.43). Regrettably, these findings have not had a substantial effect on the enhancement of lung function. Administration of vitamin D for an extended period of study may result in improved outcomes in enhancing lung function.

Plasma HDAC2 levels show a substantial increase within 3 months following vitamin D therapy.

The research findings suggest that the treatment of vitamin D for a duration of three months resulted in a notable alteration in HDAC2 levels both before and after the study (1.50 ± 1.02 vs 3.90 ± 1.39 , $P=0.006$). The results indicate that vitamin D supplementation is helpful in raising vitamin D levels and improving lung function as seen by an increase in pulmonary function test scores, however the observed differences were not statistically significant.

Table 1 COPD patient's lung function tests and after vit-D 5000iu treatment.

Characteristic	Pre (n=5)	Post (n=5)	P-Value
Age ($\pm$ mean)		61	
Pulmonary function tests (mean $\pm$ SD)			
VC	59.4 ± 9.23	72.4 ± 19.16	.145
FVC	55 ± 20.94	67.8 ± 22.9	.158
FEV1	40 ± 5.43	56.6 ± 20.05	.096
FVC/ FEV1	76.8 ± 18.71	85.00 ± 19.65	.312
Vit-D levels measure (mean $\pm$ SD)			
Vit-D levels (ng/mL)	7.63 ± 2.73	14.26 ± 2.43	.023
HDAC2 measure (mean $\pm$ SD)			
HDAC2 levels (ng/mL)	1.50 ± 1.02	3.90 ± 1.39	.006

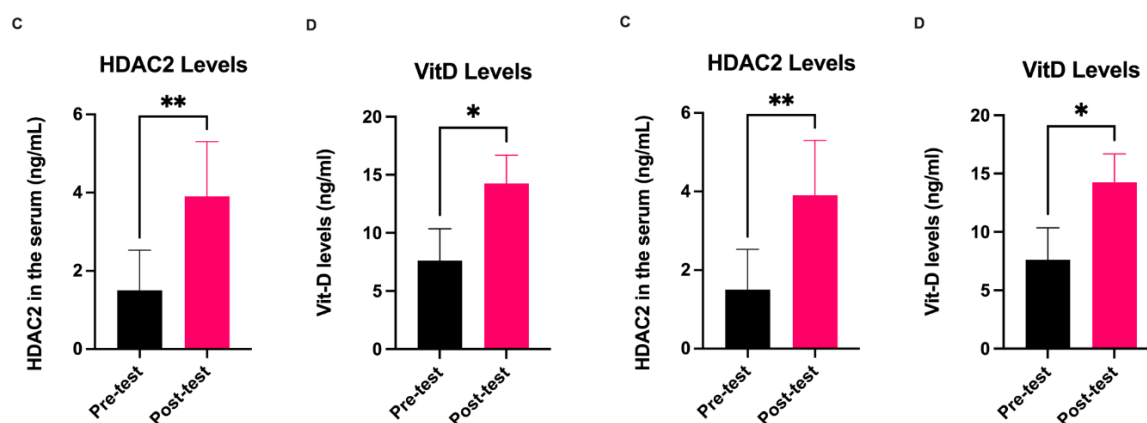


Figure 1 Vit-D 5000iu effect in VitD and HDAC2 serum levels after 3 months administration. A. Increased HDAC2 level. B. Increased VitD level. C. Significant HDAC2 different pre-post. D. Significant VitD different pre-post. Data represented as mean $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$.

DISCUSSION

Supplementing with 5000 IU of Vitamin D substantially boosts vitamin D levels during a span of 3 months.

Additionally, a study conducted at RSI Jemursari demonstrated that 25(OH)D levels increased from 7.63 ± 2.73 ng/mL prior to supplementation to 14.26 ± 2.43 ng/mL following Vitamin D supplementation. In elderly patients, daily supplementation with a Vitamin D dose of 5000 IU has been demonstrated to elevate

25(OH)D levels to over 85 nmol/L after three months. This level is deemed adequate to maintain the optimal function of Vitamin D in the body (Mastaglia et al., 2006).

In the meta-analysis conducted by Li et al., (2020), the frequency of exacerbations in patients with Chronic Obstructive Pulmonary Disease (COPD) was significantly reduced by Vitamin D supplementation, particularly in those with severe Vitamin D deficiency and low Vitamin D levels (<25 nmol/L) (Jolliffe et al., 2018).

Vitamin D is essential for COPD due to its complex mechanisms, which include the reduction of inflammation and the modulation of the immune system. Vitamin D inhibits the NF- κ B signalling pathway, which is involved in excessive inflammatory processes, due to its anti-inflammatory properties. Decreased respiratory function, increased exacerbations, and hospitalisations are all linked to vitamin D deficiency. Furthermore, Vitamin D increases the expression of VDR (Vitamin D Receptor) in type II alveolar epithelial cells, which promotes surfactant synthesis and mitigates oxidative stress in the airways (Li et al., 2020).

Plasma HDAC2 levels show a substantial increase within 3 months following vitamin D therapy.

In patients with Chronic Obstructive Pulmonary Disease (COPD), HDAC2 is a critical regulator of inflammation. By suppressing NF- κ B activity through histone deacetylation, HDAC2 reduces the activity of inflammatory genes, thereby inhibiting the expression of pro-inflammatory genes. The reduction of HDAC2 in COPD is linked to increased oxidative stress and cigarette smoke exposure, which speed up the degradation of HDAC2 by phosphorylating and nitrosylating specific residues. As corticosteroids are the primary treatment for COPD management, this condition exacerbates the patient's response to them (Zwinderman et al., 2019).

The levels of HDAC2 in the blood increased from 1.50 ± 1.02 ng/mL to 3.90 ± 1.39 ng/mL, as indicated by this study. Recent research has demonstrated that Vitamin D supplementation has a substantial impact on the improvement of respiratory function in patients with Chronic Obstructive Pulmonary Disease (COPD). A study conducted at RSI Jemursari showed that stable COPD patients experienced a substantial increase in HDAC2 levels ($p = 0.006$) because of Vitamin D supplementation for three months. This increase contributes to the reduction of histone acetylation and the expression of pro-inflammatory genes. These results indicate that Vitamin D may improve corticosteroid sensitivity, which may alleviate inflammation in COPD patients (Li et al., 2020).

The corticosteroid sensitivity of COPD patients is improved by the increase in HDAC2 levels, which in turn enhances the control of inflammation. As a result, the HDAC2 pathway has the potential to modulate inflammation and enhance clinical outcomes in COPD patients through vitamin D supplementation (Liao et al., 2020).

CONCLUSION

Vitamin D has the potential to reduce inflammation in COPD patients by enhancing corticosteroid sensitivity and functioning as an immunomodulator, as concluded by this study. Consequently, the optimal therapeutic benefits of long-term Vitamin D supplementation at the appropriate dosage in the management of COPD can be achieved by delaying the progression of the disease through increased HDAC2 levels.

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