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THE EFFECT OF VITAMIN D SUPPLEMENTATION ON PLASMA MALONDIALDEHYDE (MDA) LEVELS IN STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) PATIENTS

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ABSTRACT:

Background: Chronic Obstructive Pulmonary Disease (COPD) has become the third leading cause of death worldwide. Moreover, COPD is also a major cause of decreased quality of life in patients, with a significant morbidity rate. Without proper prevention and treatment efforts, COPD can become a global health economic burden due to high mortality and morbidity rates. Vitamin D is known as one of the antioxidant micronutrients that can prevent molecular damage and potentially halt the progression of COPD, as indicated by a decrease in Malondialdehyde (MDA). However, the role of high-dose vitamin D in maintaining stable COPD levels, specifically its impact on plasma MDA levels, is still unknown.

Methods: The participants in the study were COPD patients with GOLD 2 and GOLD 3 classifications, those who routinely took bronchodilator medication, and those whose 25(OH)D levels were less than 32 ng/ml. Patients were instructed to take 1000 IU of vitamin D orally for three months. We used paired T-tests to look at vitamin D and MDA levels.

Results: The study found that administering 1000 IU of vitamin D supplements for three months significantly increased and decreased MDA levels ($p<0.05$).

Conclusion: In patients with stable COPD, high-dose vitamin D can inhibit oxidative stress and function as an antioxidant.

Keywords: Vitamin D, MDA, MMP9, COPD

1. INTRODUCTION

According to GINA (Global Initiative for Asthma), COPD is a heterogeneous lung condition characterized by chronic respiratory symptoms such as dyspnea (shortness of breath), cough, sputum production, and/or exacerbations. This condition is caused by abnormalities in the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema), resulting in persistent and often progressive airflow obstruction.[1]

Oxidative stress is understood to be a significant predisposing factor in the pathogenesis of COPD. The progression of COPD has the confidence to arise from prolonged oxidative stress through the formation of highly oxidative carbonyl stress. Oxidants from the environment and cellular sources cause tissue damage through lipid peroxidation and oxidation of proteins and carbohydrates, forming carbonyl stress. Carbonyl stress leads to non-enzymatic post-translational modifications of proteins that can alter protein function and generate the formation of danger-associated molecular patterns (DAMPs). Damage to mitochondrial proteins due to carbonyl stress drives endogenous reactive oxygen species (ROS) production due to mitochondrial stress.[2]

At first, compensatory systems can reduce oxidative stress induced by external and internal sources. The presence of healthy lungs enables the production of endogenous antioxidants,

including superoxide dismutase, catalase, and glutathione peroxidase. These antioxidants are a biological defense mechanism against oxidative stress, specifically when cigarette smoke triggers. Nuclear factor E2-related factor 2 (Nrf2) plays a crucial role in the antioxidant system by activating genes responsible for producing antioxidants.[3]

Currently, no medication exists that can reverse or even reduce the course of COPD. Bronchodilators are the primary treatment for COPD, effectively alleviating symptoms, particularly during acute episodes. Although effectively used to reduce inflammation in asthma, inhaled corticosteroids provide limited therapeutic benefits for chronic obstructive pulmonary disease (COPD). Inhaled corticosteroids have a minor impact on the frequency of COPD exacerbations and fail to reduce the inflammatory response adequately.[2] The elevation in systemic oxidative stress is recognized to induce resistance to corticosteroid therapy due to the dysfunction of HDAC2, which plays a crucial role in dampening the inflammatory reaction. As a result, treatment becomes ineffective, leading to gradual lung damage.[4]

The role of antioxidants in vitamin D has been extensively studied, ranging from molecular to clinical levels. Physiological concentrations of the active form of vitamin D or 25(OH)D is known to increase Nrf2 levels, a crucial antioxidant regulator within the cell.[5] The role of antioxidants in vitamin D has been extensively studied, ranging from molecular to clinical levels. Physiological concentrations of the active form of vitamin D or 25(OH)D is known to increase Nrf2 levels, a crucial antioxidant regulator within the cell.[6]

A previous study conducted by Omar et al. found that taking vitamin D supplements led to an increase in antioxidant indicators such as SOD, GSH, and TAC. The study additionally found a substantial inverse correlation between plasma vitamin D levels and MDA. These findings indicate that inadequate amounts of vitamin D can increase the risk of oxidative stress in long-term illnesses. Calcitriol has demonstrated the ability to improve the removal of reactive oxygen species (ROS) by raising the amount of reduced glutathione (GSH) within cells. Part of this is achieved, in part, by regulating the expression of glutathione reductase (G.R.) and glutamate-cysteine ligase (GCL) genes. Co-administration of vitamin D and calcium supplements effectively decreases malondialdehyde (MDA) levels and results in a significant elevation in plasma GSH and overall antioxidant capacity in comparison to the separate administration of calcium and vitamin D supplements.[7]

When ingested in appropriate quantities and over an extended length of time, vitamin D appears to help prevent acute exacerbations in COPD patients.[8] Oxidative chemicals in COPD triggers, such as cigarette smoke, stimulate intracellular signaling pathways such as NF-B and MAPK p38, which are required for the initiation of inflammation and cellular oxidative stress. The increased inflammation causes the release of pro-inflammatory cytokines and chemokines such as IL-1, IL-6, IL-8, TNF-, and MCP-1, resulting in systemic inflammation and oxidative stress. It is known that vitamin D protects against inflammation, oxidative stress, and lung tissue damage by inhibiting the activation of the pro-fibrotic mediator TGF-β and the NF-κB and MAPK p38 pathways.[9]

This study aims to determine the effect of high-dose vitamin D supplementation (1000 IU) on the reduction of oxidative stress in COPD patients, measured by plasma MDA levels.

2. MATERIAL AND METHODS

An experimental design with a pre and post-test procedure used in this study. And we have used SPSS type 22 for analyizing the data. The levels of MDA will be evaluated before and after the delivery of 1000 IU of vitamin D throughout 3 months. The study will be conducted at the Respiratory Clinic of the Islamic Hospital Jemursari Surabaya, from March to October 2023. The study population includes individuals with Chronic Obstructive Pulmonary Disease

(COPD) who are receiving treatment at the Islamic Hospital Jemursari Surabaya. The participants were selected randomly, ensuring they fit the inclusion and exclusion criteria. The study's inclusion criteria for COPD patients are as follows: diagnosed with GOLD 2 or GOLD 3 COPD, undergoing regular medication and standard bronchodilator therapy, willing to sign informed consent, 25(OH)D level of 32 ng/ml, male gender, and aged 40-80 years. Patients who do not adhere to a vitamin D supplement regimen for two consecutive weeks, stop, or change their address and subsequently become unreachable will be classified as dropouts.

Pulmonary Function Test

Pulmonary function tests are conducted using a calibrated spirometer for volume and flow at least once a week. The mouthpiece and nose clip are single use. Patient conditions: No smoking for at least 2 hours before the examination, should not overeat just before the examination, should not wear overly tight clothing, short-acting bronchodilator use should be at least 8 hours prior to the examination, and long-acting bronchodilator use should be at least 24 hours prior. The examination procedure includes measuring height and determining the predicted values based on the standard lung function values of the Pneumobile Project Indonesia. The examination is then performed standing, assessing VC, FVC, FEV1, and FEF25-75.

MDA Examination

Pulmonary function tests are conducted using a calibrated spirometer for volume and flow at least once a week. The mouthpiece and nose clip are single-use. Patient conditions: No smoking for at least 2 hours before the examination, should not overeat just before the examination, should not wear overly tight clothing, short-acting bronchodilator use should be at least 8 hours prior to the examination, and long-acting bronchodilator use should be at least 24 hours prior. The examination procedure includes measuring height and determining the predicted values based on the standard lung function values of the Pneumobile Project Indonesia. The examination is then performed standing, assessing V.C., FVC, FEV1, and FEF25-75. Apart from that, MDA has procedures, such as the first to weigh the liver at 0.1 g. Then crushed in mortal and added 1 ml of distilled water. The grinding results will be put into a microtube and 100 µl TCA, 250 µl HCL and 100 µl Na-Thio added. After that it was covered with parafilm. Then heated in a water bath at 100 C for 20 minutes. After cooling, centrifuged at 3500 rpm for 10 minutes. After that, the supernatant was transferred into a microtube. and the absorption was measured with a spectrophotometer at a wavelength of 532nm.

Vitamin D Level Examination

The examination of vitamin D levels follows the Enzyme-Linked Immunosorbent Assay (ELISA) principle using the Human 1,25-dihydroxyvitamin D(3) 24-hydroxylase Elisa kit (B.T. Lab: Cat.No. E1981 Hu). The plate is pre-coated with human CYP27B1 antibodies, and samples are added, binding to the antibodies coated on the well. Biotinylated human CYP27B1 antibodies are added and bind to CYP27B1 in the sample. Streptavidin-HRP is added and binds to biotinylated human CYP27B1 antibodies. After incubation, unbound Streptavidin-HRP is washed away during the washing steps. The substrate solution is added, and color develops proportionally to the amount of human CYP27B1. The reaction is terminated by adding an acid-stop solution, and absorbance is measured at 450 nm.

Matrix Metalloproteinase-9 Examination

Serum MMP-9 levels were measured using the Quantikine enzyme-linked immunosorbent assay (ELISA). Serum concentrations of TIMP1 and TIMP2 complexes were measured with DuoSet ELISA. All reagents were stored at room temperature before use. Each analysis was performed according to the instructions provided by the manufacturer. Serum samples must be diluted one hundredfold or undiluted to identify MMP-9. Epoch microplate reader can check absorbance at 450 nm as the primary wavelength and 540 nm as a reference wavelength. Gen

5 software calculates the protein concentration in the sample. The last part is done using the standard curve equation.

3. RESULTS

Table 1. COPD patient characteristics before and after vit-D 1000iu treatment

Characteristic	Pre (n=5)	Post (n=5)	Std Deviation	P-Value
Age (±mean)	61			
Pulmonary function tests				
VC	70.2	73.0	1.2	0.80
FVC	69.2	68.6	2.15	0.795
FEV1	52.0	51.4	4.98	0.910
FVC/ FEV1	77.78	72.8	9.19	0.617
Vit-D levels measure				
Vit-D levels (ng/mL)	8.6386	14.1222	2.16	0.005
Oxidative stress measure				
MDA levels (ng/mL)	5.04	0.85	0.741	0.005
MMP9 levels (ng/mL)	1298.08	383.25	646.89	<0,001

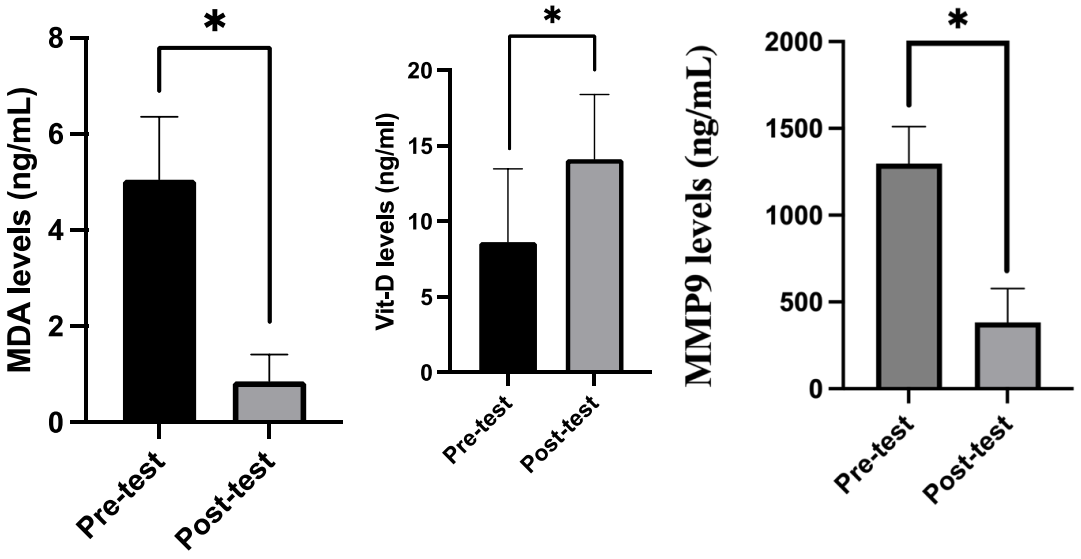

Figure 1. A. The results of the examination of plasma MDA levels show a significant difference before and after the administering 1000 IU of vitamin D. B. The results of the examination of plasma vitamin D levels indicate an increase in vitamin D levels before and after the administration of 1000 IU of vitamin D. C. The results of examination of plasma MMP-9 levels showed notable changes before and after the administering 1000 IU of vitamin D.

Based on Table 1, it is known that the average age of the patients is 61 years. The pulmonary function profile shown in Table 1 indicates a moderately mixed obstructive (FEV1% 30-60) and mildly restrictive (FVC: 60-75) lung function impairment with nonsignificant differences between pre and post-tests (P>0.05).

Administration of 1000 IU of vitamin D for three months has been shown to increase serum vitamin D levels and reduce MDA levels.

From Table 1 and Figure 1B, it can be observed that the administration of 1000 IU of vitamin D can increase serum vitamin D levels by approximately 12.94% or 1.828 ng/uL per month.

Unfortunately, after three months of vitamin D therapy is 14.1222 ng/mL (35.305 nmol/L), which is still insufficient for vitamin D requirements. Normal vitamin D levels in the blood should be maintained above 20 ng/mL (50 nmol/L) to meet daily vitamin D needs. This result may be due to the initially low vitamin D levels, so the administration of vitamin D increases vitamin D levels but does not reach average values. This is supported by the fact that one patient successfully reached normal levels because they had a higher baseline value than others.

Based on Table 1 and Figure 1A, the examination results of MDA levels show a drastic decrease after the administration of 1000 IU of vitamin D. Vitamin D is believed to reduce MDA levels by around 27.7% or 1.396 ng/mL per month. These results support the assumption that a 12.94% increase in vitamin D levels in the blood leads to a progressive 27.7% decrease in MDA levels.

A dosage of 1000 IU of vitamin D does not rapidly improve lung function, but it promptly improves oxidative stress, as indicated by a progressive reduction in MDA levels.

Based on Table 1, it is evident that the lung function profile indicates a moderate mixed obstructive impairment (FEV1% 30-60) and mild restrictive impairment (FVC: 60-75) with non-significant pre and post-test differences (P>0.05) after the administration of 1000 IU of vitamin D. These results also provide evidence that vitamin D cannot improve overall lung impairments but can prevent the onset of new damage caused by oxidative stress. This is demonstrated by the ability of vitamin D to inhibit MDA as a marker of oxidative stress in the blood.

4. DISCUSSION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by persistent airflow limitation. Since oxidative stress is recognized as a significant predisposing factor in the pathogenesis of COPD, several antioxidant-based therapies were developed to prevent the worsening of COPD. Several antioxidant agents such as Nrf2 activators, N-acetyl-L-cysteine (NAC), N-acystelyn (NAL), N-isobutyrylcysteine (NIC) and other catalytic antioxidants have successfully reduced oxidative load and inflammatory reactions in the lungs.[10] Vitamin D, as a source of potent antioxidants, is known to have great potential in improving COPD symptoms. Studies in COPD populations suggest that Vitamin D may be beneficial in reducing acute exacerbations if consumed in sufficient amounts and over a long period.[8] According to the findings of this study, there are discrepancies compared to a meta-analysis study on the impact of vitamin D on COPD lung function measures. The meta-analysis study demonstrated positive changes in lung function, including higher FEV1 and FEV1/FVC, as well as reduced exacerbation rates, following vitamin D supplementation. Unfortunately, the recommended dose that would effectively initiate improvements in lung function is not specified.[11]

Based on the results of Table 1, there is an increase in vitamin D levels after being given vitamin D 1000. Vitamin D levels given for three months show a progressive increase in serum vitamin D, which aims to meet daily vitamin D needs, especially in preventing oxidative stress in COPD. Unfortunately, the increase in vitamin D values in patients was not optimal, where average vitamin D values should have a cutoff of 50 nmol/L,[12] or 75 nmol/L.[13] The most recent consensus indicates that the objective of vitamin D administration for therapeutic purposes is to prevent blood levels of 25(OH)D from falling below 30 nmol/l or 12 ng/mL, and to achieve values above 50 nmol/l. By maintaining blood levels of 25(OH)D above 30 nmol/l, the elderly can prevent potential health issues such as decreased bone mineral density, osteomalacia, and fractures. Possible non-skeletal consequences may encompass increased susceptibility to falls, diminished muscular power, diabetes, cancer, cardiovascular disease, and, notably, COPD.[14]

The study found that the average baseline level of vitamin D for the Elderly population is 8.63 ng/mL or 21.59 nmol/L. This value differs greatly from the consensus target, suggesting that the older population is very susceptible to vitamin D insufficiency, which in turn exacerbates their COPD symptoms. In a recent study conducted by Chalcraft and his colleagues, calculated an age-related reduction in vitamin D production of 13% per decade, demonstrating that production at 70 years is half that at 20 years.[15] Various variables believed to cause vitamin D deficiency in older individuals are associated with the reduced ability of vitamin D to stimulate calcium absorption in the gastrointestinal tract and the decline in renal function that occurs with age.[16]

The 1000 iu dose in this study aims not only to increase vitamin D levels but also to avoid the risk of hypercalcemia and vitamin D toxicity and prevent falls, especially in the elderly.[17,18] A meta-analysis study demonstrated that administering moderate doses of vitamin D (700–1000 IU per day) can potentially decrease the likelihood of falling in older persons with vitamin D deficiency.[19] In the placebo-controlled multi-dose experiment, conducted on menopausal women with initial 25(OH)D levels below 50 nmol/L, it was found that administering low-dose vitamin D on a daily basis had a more positive impact on reducing the risk of falls compared to daily doses of 4000 and 4800 iu.[20] However, the administration of vitamin D necessitates dose adjustment as a result of the heterogeneity in individual reactions to vitamin D.[21] In a meta-regression analysis of individual participants from seven winter based RCTs conducted by Cashman and colleagues, they found that the daily dose required to prevent severe deficiency (specifically, attaining a level of 25 nmol/l in 97.5% of persons) was 400 iu. To achieve a safer level of 50 nmol/l, a daily intake of 1000 IU is required. However, it should be noted that this dosage exceeds the previous recommendations set by the Institute of Medicine (IOM) and other regulatory organisations.[22]

In this study, administration of Vitamin D at 1000 IU showed a significant antioxidant capacity, as seen by a gradual reduction in MDA levels. Multiple studies evaluating the impact of Vitamin D on MDA have demonstrated a noteworthy influence of Vitamin D supplementation on MDA levels. A recent meta-analysis study demonstrated consistent findings, indicating a substantial decrease in MDA levels following Vitamin D dosing. The meta-analysis study revealed that patients with COPD regularly exhibit elevated blood concentrations of MDA in comparison to healthy controls. This suggests that lipid peroxidation, and consequently oxidative stress. [23] plays a crucial role in the development of COPD.[24] Studies investigating the impact of vitamin D on COPD have found that higher levels of serum 25(OH)D are linked to a lower risk of morbidity and mortality from COPD. This suggests that vitamin D may have a protective effect in the development of COPD.[25]

Administration of VD showed its antioxidant ability as indicated by a progressive decrease in MDA levels. Further research is required to establish a more consistent correlation between Vitamin D and MDA.[26] Our result contradicts the recent meta-analysis that found no significant difference in the lowering of MDA levels between daily Vitamin D therapy versus dosing every two weeks or once a month. The study demonstrated that administering Vitamin D at a dosage of less than 100,000 units per month did not effectively reduce MDA readings.[27] Nevertheless, there is a scarcity of journals that explicitly elucidate the impact of Vitamin D on MDA levels in COPD. Furthermore, the administration of vitamin D is recognised for its ability to decrease MDA levels through the activation of Nrf2, which in turn stimulates the production of antioxidant genes.[28,29]

Matrix Metalloproteinase-9, or Gelatinase B, has an active molecular weight of 85 kDa. Pro-MMP-9 and -13, gelatin, elastin, collagens IV, V, VII, X, and XIV are some of its possible substrates.

Numerous research on humans have looked for connections between MMP-9 and COPD. MMP-9 levels in plasma have been elevated in COPD and α1-trypsin deficiency-associated emphysema[33,34]. They also showed a negative correlation with oxygen saturation, FEV1, and carbon monoxide transfer factor. Furthermore, MMP-9 levels could predict the number of exacerbations and a decline in pulmonary function. According to induced sputum analysis, smokers with and without airway obstruction had higher MMP-9 protein and MMP-9 activity. Interestingly, MMP-9 levels in the sputum rose upon quitting smoking relative to baseline, and this rise was unrelated to the quantity of neutrophils present[34]. It has been observed that the lungs of smokers with COPD[35] and guinea pigs exposed to cigarette smoke exhibit elevated immunohistological staining of MMP-9. It has been demonstrated that cigarette smokers' alveolar macrophages release higher baseline and stimulated quantities of MMP-9[36].
The administration of vitamin D levels caused a significant decrease in antioxidant MMP-9 levels.. According to PCR analysis of bulk lung samples, MMP-9 is overexpressed in smokers with severe COPD. There are positive associations with arterial carbon dioxide tension and the diffusing capacity of the lung for carbon monoxide and oxygen and negative correlations with FEV1. Through laser capture microdissection, Gosselink et al.[38] discovered that the advancement of GOLD categories of COPD was connected with an elevation of MMP-9 gene expression in the parenchyma. In patients with COPD, urokinase plasminogen activator and its receptor, genes linked to MMP overexpression, were shown to be expressed more often[37] in a different microarray analysis.The study may have limitations related to the characteristics of the participants. For example, the study only includes patients with a specific severity of COPD or excludes patients with comorbidities. In that case, the findings may not apply to a broader population of COPD patients. Including a more diverse range of participants would enhance the generalizability of the results.

5. CONCLUSION

Administering a daily dose of 1000 IU of vitamin D for a period of three months effectively raised daily vitamin D levels, therefore preventing the risk of vitamin D deficiency, which can exacerbate the severity of COPD. Furthermore, it shows the capacity to inhibit and decrease MDA levels, a biomarker of oxidative stress caused by lipid peroxidation, which is recognized to be associated with the development of chronic obstructive pulmonary disease.

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Disclosure
The author reports no conflicts of interest in this work.

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