The relationship between forced expiratory volume 1 (FEV 1) with 25(OH) vitamin D level and hs-CRP in COPD in H. Adam Malik General Hospital Medan

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ABSTRACT

Background: The number of people with COPD according to WHO was increasing to 400 million people by 2020 and half of these occur in Indonesia. The incidence of COPD in Indonesia ranks 5th highest in the world at 7.8 million. COPD was a non-communicable disease that is thought to be closely related to the increasing number of smokers, especially in young age groups. This study aims to determine between FEV1 with 25 (OH) vitamin D level and hs-CRP in COPD patients.

Methods: This study was a cross-sectional method conducted in H. Adam Malik General Hospital Medan, from January to June 2018 on 51 COPD patients who were treated at Pulmonology Outpatient Clinic. Spirometry examination, 25 (OH) levels of vitamin D, and hs-CRP was

examined. Data were analyzed statistically using SPSS version 16 for windows.

Results: Total 51 patients who participated in the study were all male. Based on Pearson Correlation Test, FEV1 value of COPD patients did not show a significant correlation with levels of 25 (OH) vitamin D. While the Spearman Rank Correlation Test shown significant correlation with hs-CRP levels. Anova test results and Kruskal Wallis test on levels of 25 (OH) vitamin D, hs-CRP and Leukocyte counts shown no significant differences with GOLD criteria.

Conclusion: The mean FEV1 value of COPD patients, 25 (OH) levels of vitamin D and the number of Leukocytes shown no significant statistical difference, whereas the higher the FEV1value, the lower the hs-CRP.

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INTRODUCTION

COPD is currently the fourth leading cause of death in the world. More than 3 million people died because COPD in 2012 accounted for 6% of all global deaths. In 2002 COPD was the fifth leading cause of death. Estimates show that COPD in 2020 is the third leading cause of death worldwide. In Indonesia, the prevalence of COPD in 2013 reached 3.7%. East Tenggara Nusa have the highest COPD prevalence which reached 10%.[1]

At the H. Adam Malik General Hospital in the period January 2015-December 2015 the total number of COPD patients was 170 people, namely 146 men (85.9%) and women 24 people (14.1%).[2]

In the study in H. Adam Malik General Hospital Medan, there was an increase in CRP levels in exacerbation COPD patients compared to stable COPD patients with levels >10 mg/l in exacerbation COPD patients and ≤ 10 mg/l in stable COPD patients.[3]

In a study of 130 stable COPD patients and 65 healthy controls reported that hs-CRP levels increased in stable COPD patients (4.1 mg/L) who did not experience repeated exacerbations within two months, especially those who remained to smoke compared to controls (1.8 mg/L). Hurst et al. studied 36 biomarkers in 90 exacerbation COPD patients whose results showed that hs-CRP was the

most selective marker, plasma CRP concentrations could be useful in confirming COPD exacerbations but could not predict the severity of exacerbations, and acute phase response to exacerbations related to function monocytes.[4,5]

Some vitamins (vitamins C, D, E, A, beta-carotene and alpha) are associated with improvements in the clinical condition of COPD patients. They found the fact that consumption of multivitamins can improve lung function, reduce exacerbations and improve clinical symptoms of patients. It is also said that high vitamin intake can prevent lung tissue damage. This was then proposed to be one of the COPD therapies, but until now there has been no empirical evidence to prove this hypothesis.[6,7]

Vitamin D has a protective effect on lung tissue. Vitamin D, which has been known for its role in bone homeostasis, can modulate the immune system in lung tissue.[8] Based on the aforementioned above, This study aims to determine between FEV1 with 25 (OH) vitamin D level and hs-CRP in COPD patients.

MATERIAL AND METHODS

This study was conducted with a cross-sectional method from January to June 2018. The population in the study were all COPD patients who

were treated at the COPD Outpatient Clinic at Pulmonology and Respiratory Department H.Adam Malik General Hospital Medan that meets the inclusion criteria and exclusion criteria. Inclusion criteria: COPD patients who were treated at the COPD outpatient clinic Pulmonology and Respiratory Department H. Adam Malik Hospital Medan, with age > 40 years and willing to participate in the study. Exclusion criteria: COPD patients in acute exacerbations, asthma patients, post TB obstruction syndrome, lung tumors, osteoarthritis, liver disease, leukocytes <4,000/μL or > 11,000/μL, taking drugs that affect levels of 25 (OH) vitamin D, are receiving vitamin D therapy, taking drugs that affect levels of hs-CRP (statins, vitamin C, vitamin E, antibiotics and steroid classes). FEV1 was measured in percentage (%), vitamin D in ng/mL, and hs-CRP in mg/L. Data were analyzed statistically using SPSS version 16 for windows.

RESULT

The study was conducted at the Clinical Pathology Department of H. Adam Malik General Hospital Medan/Faculty of Medicine Universitas Sumatera Utara in collaboration with the Department of Pulmonology and Respiration H. Adam Malik General Hospital Medan/Faculty of Medicine Universitas Sumatera Utara. This study involved 51 patients with a stable diagnosis of COPD who had met the inclusion and exclusion criteria. The samples were examined for leukocyte counts, levels of 25(OH) vitamin D and levels of hs-CRP. The collected data is presented in table form.

In Table 1 shows the characteristics of the study subjects in the form of age, occupation, Brinkman index, FEV1, levels of 25(OH) vitamin D, and levels of hs-CRP. In this study, it was seen that all study respondents were male (100%). Respondents in the age range 60-69 years were 26 people (51%). The average age of respondents in this study was 64.05 ± 8.05 years. The majority of respondents, as many as 28 people (54.9%) are retired/not working, as many as seven people (13.8%) work as traders. Based on the Brinkman index there were four people (4.7%) in the medium category (200-599) and 47 people (92.2%) in the weight category (≥600). Based on FEV1, 24 people (47.1%) had

Table 1   Baseline characteristics of respondents

Variable		N (%)	Mean±SD/ Median (Min-Max)
Gender	Male	5 (100)	
	Female	0 (0)	
Age	40-49 years	2 (3.9)	64.05± 8.05 years
	50-59 years	11 (21.6)	
	60-69 years	26 (51.0)	
	≥70 years	12 (23.5)	
Occupation	Retired	28 (54.9)	
	Labour	4 (7.8)	
	Employees	5 (9.8)	
	Traders	7 (13.8)	
	Drivers	4 (7.8)	
	Farmers	3 (5.9)	
Brinkman index	200-599	4 (7.8)	
	≥600	47 (92.2)	
FEV1	50%≤ FEV1<80%	7 (13.7)	33.65 ± 15.78
	30%≤ FEV1<50%	20 (39.2)	
	FEV1<30%	24 (47.1)	
25(OH) vitamin D	< 20 ng/mL	8 (15.7)	27.57 ± 6.74
	20-29.9 ng/mL	23 (45.1)	
	30-100 ng/mL	20 (39.2)	
	>100 ng/mL	0 (0)	
hs-CRP	< 10 mg/L	51 (100)	0.34 (0.02-2.16)
	≥ 10 mg/L	0 (0)	

Table 2   FEV1 correlation test with 25 (OH) vitamin D, leukocytes and hs-CRP

Variables	FEV1	
	r	P
25 (OH) Vitamin D	-0.131	0.180*
Leucocytes	-0.112	0.217*
hs-CRP	0.260	0.032**

*Pearson Correlation Test;**Spearman Rank Correlation Test; P-value is significant if < 0.005

Table 3   Results of different test levels of 25 (OH) vitamin D, number of leukocytes and levels of hs-CRP based on GOLD criteria

Variable	GOLD	n	Mean±SD	P
Leukocytes	2	7	7,458.57±1,436.83	
	3	20	8,053.5 ±1,922.71	0.603*
	4	24	8,253.33 ± 1,847.99	
25(OH) vitamin D	2	7	24.01 ± 3.81	
	3	20	27.35 ± 6.56	0.256*
	4	24	28.79 ± 7.33	
hs-CRP	2	7	0.21 ± 0.13	0.122**
	3	20	0.37 ± 0.46	
	4	24	0.633 ± 0.632	

*Anova Test; **Kruskal Wallis Test; Significant p<0.005

FEV1<30%, as many as 20 people (39.2%) had a value of 30%≤FEV1<50%, as many as 7 people (13.7%) had a value of 50%≤FEV1<80%, and no study sample had a VEP1 value> 80%. The average value of FEV1respondents in this study was 33.65 ± 15.78%. Based on 25 (OH) levels of vitamin D as many as 23 people (45.1%) had levels of 25 (OH) vitamin D ranging from 20-29.9 ng/mL, as many as 20 people (39.2%) had levels of 25 (OH) vitamin D ranges from 30-100 ng/mL. The average level of 25 (OH) vitamin D respondents in this study were 27.57 ± 6.74 ng/mL. Meanwhile, all respondents had hs-CRP levels that were <10 mg/L. The median value of the respondent's hs-CRP level in this study was 0.34 mg/L, with a minimum value of 0.02 mg/L and a maximum value of 2.16 mg/dL.

In Table 2 shows the correlation between FEV1 values with levels of 25(OH) vitamin D, the number of Leukocytes and hs-CRP. To see the relationship between FEV1 values with levels of 25(OH) vitamin D and the number of leukocytes used Pearson correlation test. It was found that the relationship between the FEV1 value of the study respondents showed no significant negative correlation with levels of 25(OH) vitamin D and the number of Leukocytes. Between FEV1 with levels of 25(OH) vitamin D obtained the value of r = -0.131 and p-value = 0.180 while between FEV1 and the number of leukocytes obtained the value of r = -0.112 and the value of p = 0.217. Meanwhile, to see the relationship between FEV1 scores of

respondents with hs-CRP levels, the Spearman Rank correlation test was performed. The relationship between FEV1 values of research respondents showed a significant negative correlation with hs-CRP levels with r = -0.260 and p = 0.032. This value indicates that the higher the FEV1 value, the lower the hs-CRP and vice versa.

COPD patients in this study were classified according to the degree of airway obstruction he suffered based on the FEV1 value obtained from spirometry examination. This classification is based on GOLD criteria, namely GOLD-1 with mild obstruction (FEV1≥ 80% prediction), GOLD-2 with moderate obstruction (50% ≤ FEV1 <80% prediction), GOLD-3 with severe obstruction (30% ≤ FEV1 < 50% prediction) and GOLD-4 with very severe obstruction (FEV1 <30% prediction).

Of the 51 COPD patients examined there were seven people including GOLD-2, 20 people including GOLD-3, and 24 people including GOLD-4. Nothing belongs to GOLD-1 (Figure 1).

By using the ANOVA test, different leukocyte counts and 25(OH) vitamin D levels of in COPD patients were classified according to GOLD. For the number of leukocytes, the mean values were 7,458.57 ± 1,436.83 in the moderate obstruction group (GOLD-2), the mean of 8,053.5 ± 1,922.71 in the severe obstruction group (GOLD-3) and the mean value of 8,253.33 ± 1,847.99 in the very severe obstruction group (GOLD-4). Levels of 25(OH) vitamin D obtained mean values 24.01 ± 3.81 in
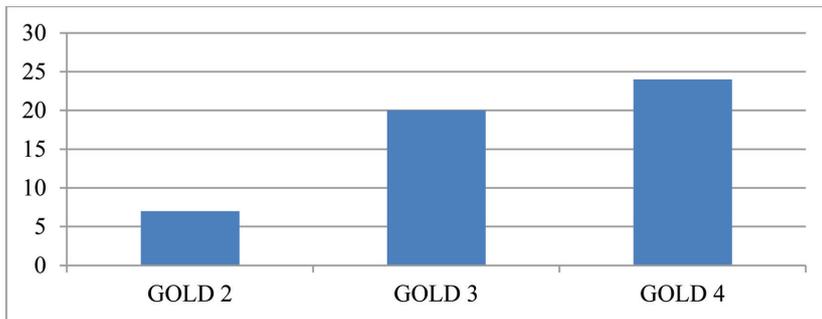
Figure 1 Classification of COPD patients based on GOLD criteria

the moderate obstruction group (GOLD-2), mean 27.35 ± 6.56 severe obstruction group (GOLD-3) and mean value 28.79 ± 7.33 in the very severe obstruction group (GOLD-4). P value = 0.603 for the number of Leukocytes and p = 0.256 for 25 (OH) vitamin D where this value states that there is no significant difference in the number of leukocytes and 25(OH) levels of vitamin D between the moderate obstruction group (GOLD-2), heavy (GOLD-3) and very heavy (GOLD-4).

By using the Kruskal Wallis test different levels of hs-CRP were tested in COPD patients who had been classified according to GOLD. The mean value was 0.21 ± 0.13 in the medium obstruction group (GOLD-2), the mean was 0.37 ± 0.46 in the severe obstruction group (GOLD-3), and the mean value was 0.633 ± 0.632 in the very severe obstruction group (GOLD -4). With p = 0.122 for hs-CRP level where this value states that there is no significant difference in hs-CRP level between the moderate obstruction group (GOLD-2), weight (GOLD-3) and very heavy (GOLD-4).

DISCUSSION

This study involved 51 male patients who had been diagnosed as COPD patients who had undergone pulmonary treatment at Haj. Adam Malik General Hospital Medan. The subjects of the study were patients who had treatment from January 2018 to June 2018. In table 1 it was seen that the mean age of COPD patients was 64.05 ± 8.05 years with the highest age ranging from 60-69 years. This is consistent with the results stated in several previous studies that the prevalence of COPD is higher in those aged >40 years and more in men than women, although in this study all the subjects of the study were men.[10,11] The high age of this patient is caused by several factors including the increase in life expectancy and the longer the exposure time to risk factors. The host factor itself is thought to be strongly associated with the incidence of COPD, namely the increasing number of smokers, as well as the increase in indoor and outdoor air pollution, especially in the workplace.[10,12]

Table 1 also shows that the FEV1<30% is the highest, which is 47.1% with the average FEV1 value being 33.65 ± 15.78%. This shows a decrease in FEV1 values in the COPD subjects examined. The lower the FEV1 value shows the worse the obstruction.[13]

In this study, it was found that the highest Brinkman (IB) index was in the weight group (≥ 600). Based on Ohno et al. 's research on 61 patients with COPD in 2007, all patients with severe and very severe COPD had IB: 990 ± 427.[14] Nugraha in his study in 2010 in 40 patients with COPD showed that according to IB patients with COPD mild degree with IB 30%, moderate to IB 50% and severe degree with IB 20%. While patients with severe COPD or severe weight has a low IB of 5%, IB is 25%, IB weighs 70%.[15] Based on Syamsul Bihar's research in 2012, the most IB is a value of ≥ 600 (weight) of 13 people (59.1%).[16]

The most common 25(OH) vitamin D levels in this study ranged from 20-29.9 ng/mL as much as 45.1%, with the mean level of 25(OH) vitamin D of the study subjects being 27.57 ± 6.74 ng/mL. This number illustrates the decrease in levels of 25(OH) vitamin D in the serum of COPD patients studied. According to the Endocrine Society guidelines, vitamin D status was defined as 31-60 ng/mL efficiency, calcifediol insufficiency 21-30 ng/mL and ≤ 20 ng/mL deficiency.[17] This guideline classified COPD patients in this study as belonging to the vitamin D insufficiency group.

The level of hs-CRP of COPD patients studied was still in the normal range (0.00-<10.00 mg/L) with a median of 0.34 mg/L and the minimum-maximum was 0.02-2.16 mg/ L. This level of hs-CRP in the normal range is possible because the sample is COPD patients who are in a stable condition so that CRP is also a systemic marker that is very sensitive to inflammatory reactions and tissue damage does not increase in stable COPD conditions.[18] These results are different with Gan et al., 2004 which stated that COPD patients significantly increased levels of CRP, fibrinogen, leukocytes, and TNF-α compared to healthy controls, which indicates that persistent systemic inflammation occurs in COPD even after stopping smoking.[19]

FEV1 values of COPD patients examined did not show a significant correlation with levels of 25(OH) vitamin D and the number of leukocytes of patients. Between FEV1 with levels of 25(OH) vitamin D obtained the value of r = -0.131 and p-value = 0.180 while between FEV1 and the number of leukocytes obtained the value of r = -0.112 and p = 0.217 (Table 2). In this study, 25(OH) vitamin D levels of COPD patients examined showed a lower tendency compared to normal

people (NHANES III based insufficiency) although, statistically there was no significant association with FEV1 values. This means that 25(OH) levels of vitamin D in the patient's serum are not related to the degree of obstruction or the severity of COPD suffered by the patient. This result is different from the Menon et al., 2016 study which found that vitamin D levels were associated with FEV1 values (p = 0.0016) even with the severity of COPD suffered. In patients with exacerbation frequency, vitamin D levels were lower than those with fewer exacerbations (p = 0.00001).[20]

The number of leukocytes in this study was not significantly associated with FEV1, it was possible because the selection of samples which were stable COPD. This is in line with the study of Moberg et al., 2014 who found that the number of leukocytes in COPD patients was associated with the incidence of hospitalization which usually occurs in COPD patients who experienced exacerbations with hazard ratio 1.06 (95% CI: 1.01–1.11, P = 0.018).[21]

FEV1 values were significantly negatively correlated with hs-CRP levels of COPD patients examined with r = -0.260 and p = 0.032 (Table 2). This value indicates that the higher the FEV1 value the lower the hs-CRP level and vice versa. This is in line with the results of a study of 130 stable COPD patients and 65 healthy controls who reported that hs-CRP levels increased in stable COPD patients (4.1 mg/L) compared to controls (1.8 mg/L).[4,5] Results of research conducted in Iran by Alavi et al., 2014 also showed a significant relationship between levels of hs-CRP and FEV1 (p = 0.0001) where it was also reported that hs-CRP levels were positively correlated with the severity of the disease based on GOLD criteria.[22]

In this study there were also no significant differences in 25(OH) levels of vitamin D from each group of patients based on GOLD criteria (p = 0.256). This shows that 25(OH) levels of vitamin D are not the only factor that plays a role in the severity of COPD although it is known that 25(OH) levels of vitamin D plays a role in the regulation of the body's immune system and it can be assumed that there are many factors that play a role in determining vitamin D levels. In the human body. Menon et al., 2016 also found in his study that vitamin D deficiency was found in 37.5%, 41.27%, 74.29%, and 81.82% of GOLD-1 patients to GOLD-4 in sequence with the values average lower in GOLD-3 and GOLD-4. The differences obtained also showed significant results.[20]

Leukocyte counts of COPD patients studied did not show a significant difference between each group based on GOLD criteria (p = 0,603) although there was a trend toward higher mean leukocyte counts in the GOLD-4 group compared to GOLD-3 (8253 ± 1847.99 vs. 8053 ± 1922.71) and GOLD-3 against GOLD-2 (8053 ± 1922.71 vs. 7458 ± 1436.83). Moberg et al., 2014 in his study reported that single leukocyte counts could be a predictor of mortality in COPD patients in which the study found that of 208 patients studied there were 197 (46.6%) patients with an increase in the number of leukocytes (> 8.8×10^9 / L).[21]

The level of hs-CRP of COPD patients studied did not show a significant difference between each group based on GOLD criteria (p = 0.122) although there was a trend towards higher levels of hs-CRP in the GOLD-4 group compared to GOLD-3 (0.63 ± 0.63 vs 0.37 ± 0.46) and GOLD-3 against GOLD-2 (0.37 ± 0.46 vs. 0.211 ± 0.13). This trend supports the theory that CRP as a systemic inflammatory marker can be used as a marker of the severity of COPD in addition to pulmonary physiological examination, and can also be used as a therapeutic monitoring.[22]

CONCLUSION

This study found that there was no statistically significant different among the mean FEV1 value of COPD patients, 25 (OH) levels of vitamin D and the number of Leukocytes. However this study suggest that the higher level of FEV1value had a tendency to the lower hs-CRP level.

ETHICAL CLEARANCE

Ethical approval had been conducted by Ethics of Committee at Universitas Sumatera Utara.

CONFLICT OF INTEREST

The authors declare there is no competing interest regarding manuscript.

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AUTHOR CONTRIBUTION

All authors are responsible as contributor regarding the content of manuscript.

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