Original Article

Relationship Between Level of Serum Adiponectin and Frailty in Elderly Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Elderly are prone to the health effects of chronic obstructive pulmonary disease (COPD). Frailty is a geriatrics syndrome, adiponectin is an adipokine that regulates energy. Adiponectin is affected by age. Increased adiponectin can lead to muscle wasting which will further reduce body mass index (BMI), which indirectly increases the degree of frailty. The relationship between adiponectin with frailty degree in COPD is still unknown. The aims of this study was to investigate the relationship between plasma adiponectin levels and frailty in COPD elders. This was an observational analytic cross-sectional study. All anthropometric parameters, including weight, height, and BMI, were measured. Adiponectin was measured by ELISA methods obtained from venous blood samples. Aged more than or equal to 60 years old, the patients underwent spirometry and the degree of frailty defined by the Fried criteria. Statistic analysis used Rank Spearman. Thirty-eight male COPD patients became the subject of the study. The average age was 70-74 years, with a total of 13 robust, 12 prefrails and 13 frail patients. Level of adiponectin (mean and SD) in robust, prefrail, and frail were 6.84+ 2.66 , 6.58 + 4.27, and 11.62 + 4.90 respectively, p=0.015. Further analysis showed that the level of adiponectin rose progressively with an increasing number of components of frailty. The degree of obstruction mostly with mild (42.1%), and no subjects with very severe. There was an increase in serum adiponectin levels in all subjects. In conclusion, the level of adiponectin serum correlates positively with the degree of frailty.

Keywords: *adiponectin, COPD, frailty*

ABSTRAK

Lansia sangat rentan terhadap efek kesehatan yang merugikan dari penyakit paru obstruktif kronik (PPOK). Frailty adalah sindrom geriatrik yang penting, sedangkan adiponektin adalah adipokin yang mengatur homeostasis energi. Adiponektin dipengaruhi oleh usia. Peningkatan adiponektin dapat menyebabkan pengecilan otot yang selanjutnya akan mengurangi indeks massa tubuh (IMT), yang secara tidak langsung meningkatkan derajat frailty. Hubungan antara adiponektin dengan derajat frailty pada PPOK usia lanjut masih belum diketahui. Tujuan penelitian ini adalah untuk menentukan hubungan antara kadar adiponektin plasma dan frailty pada lansia dengan PPOK. Penelitian ini adalah penelitian cross-sectional analitik observasional. Semua parameter antropometrik, termasuk berat badan, tinggi badan, dan IMT, diukur. Adiponektin diukur pada sampel darah vena dengan metode ELISA. Pasien yang berusia lebih dari atau sama dengan 60 tahun menjalani spirometri dan derajat frailty menurut kriteria Fried. Analisis statistik menggunakan Rank Spearman. Tiga puluh delapan pasien PPOK laki-laki menjadi subjek penelitian. Usia rata-rata adalah 70-74 tahun, dengan total 13 pasien robust, 12 prefrail dan 13 frail. Kadar adiponektin (rerata dan SD) pada kelompok robust, prefrail, dan frail masing-masing adalah 6,84 + 2,66, 6,58 + 4,27, dan 11,62+ 4,90, p=0,015. Analisis lebih lanjut menunjukkan bahwa kadar adiponektin meningkat secara progresif seiring peningkatan jumlah komponen frailty. Derajat obstruksi sebagian besar ringan (42,1%), dan tidak ada subjek dengan obstruksi berat. Terdapat peningkatan

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kadar adiponektin serum pada semua subjek. Sebagai simpulan, kadar serum adiponektin berkorelasi positif dengan derajat frailty.

Kata kunci: *adiponectin, PPOK, frailty*

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a typical disease of aging with a prevalence of around 12% in the age group >64 years.[1,2,3,4] In elderly who suffer from COPD, the process of this disease can also increase the level of adiponectin through inspiratory muscle mechanism that is exercised continuously (chronic exercise), thereby increasing the REE (resting energy expenditure). As a result, an increase in fatty tissue activity will release adipokine and cause an increase in plasma adiponectin levels.[5,6,7,8]

Increased severity and shortness of breath result in the inactivity of COPD patients, which in turn results in loss of muscle strength, leading to mobility problems, which contribute to the high frequency of frailty in those patients.[9,10,11] Underweight patients have an increase in REE compared to overweight and normal-weight patients, which is associated with decreased serum and adipose tissue leptin. Increased serum adiponectin also occurs, demonstrating the role of adipokines in cachexia-related energy imbalances in COPD.[12,13,14,15,16]

This study was conducted to identify the relationship between serum adiponectin levels and the degree of frailty measured using the Cardiovascular Health Study (CHS) scoring system[17], a scoring system that is most widely used and has the broadest validity to determine the degree of frailty in the population of COPD elderly patients in Surabaya.

MATERIALS AND METHODS

This study was a cross-sectional analytic study to analyze differences in serum adiponectin levels between degrees of frailty in elderly COPD patients. This study was conducted at the Pulmonary and Geriatric Outpatient Unit, dr. Soetomo Hospital, Surabaya, Indonesia. The study samples were subjects aged ≥ 60 years at the Outpatient Unit, dr. Soetomo Hospital, Surabaya, who fulfilled the inclusion criteria, ie aged over or equal to 60 years old, a Mini Mental State Examination (MMSE) score of ≥ 18, and was willing to follow the study by signing informed consent and information for consent. Criteria for the exclusion of the subjects were in acute exacerbations, had a history of diabetes mellitus, had a malignancy or history of malignancy, and had a history of stroke with limited motor function.

Measurement of Serum Adiponectin

Adiponectin is a 30 kDa glycoprotein that is secreted primarily by adipocytes and induces wide ranging paracrine and endocrine effects on metabolism and inflammation. Adiponectin circulates in the blood with a high concentration as total adiponectin[18].

Adiponectin measurement in this study used a quantitative ELISA method from venous blood samples in μg / ml units. Blood samples were taken as much as 5 ml and put into Vacuette Z Serum Sep Clot Activator tubes and store inside the cooler box with a temperature of 2–4° C, to be processed and separated the serum part in less than 24 hours by centrifugation. The total adiponectin was measured using a commercial tool kit Sekisui Medical Co., Ltd. The normal value of adiponectin serum was a range between 2.54–6.06 μg / mL. Type of data is a ratio data.

Samples were taken by consecutive sampling. A total of 38 samples were obtained[19]. All data were entered into the computer through the statistical program R version 3.1.2. Data on general

characteristics of the samples according to age, sex, level of education, degree of COPD, smoking history, and comorbid history were presented descriptively in tabular form. Subjects' specific characteristics data including body mass index, MMSE score, handgrip strength, 15 feet walking test, and PASE scores are presented in tables and graphs. Types of data were ordinal (categorical) data for frailty degrees and ratio (numeric) data for serum adiponectin levels, so we used One-Way Anova test if the parametric statistical test requirements were met, or the Kruskal-Wallis test if the parametric statistical test requirements were not met. Subanalysis was conducted to determine the relationship of serum adiponectin levels with Fried's five frailty components.

RESULTS AND DISCUSSION

General Characteristics of the Subjects

The number of subjects in this study were 38 COPD patients in the Pulmonary and Geriatric Outpatient Unit, Dr. Soetomo Hospital, Surabaya, Indonesia, who had fulfilled the inclusion and exclusion criteria. Table 1 shows the general characteristics of the study subjects.

Most subjects were found in the 70-74 years age range. The mean age of the subjects in robust group was 69.69 ± 7.85 years, in prefrail group 70.50 ± 6.85 years, and in frailty group 70.85 ± 8.19 years. All of the subjects (100%) were male.

The degree of COPD obstruction used in this study was based on the 2014 GOLD criteria which divided into 4 groups, mild (GOLD 1), moderate (GOLD 2), severe (GOLD 3) and very severe (GOLD 4) obstruction[20]. We obtained mostly COPD patients with mild obstruction degrees as many as 16 (42.1%) patients, and no subjects with COPD had very severe obstruction degrees.

Increased serum adiponectin level was found in COPD patients with severe obstruction. However, the comparative test did not show differences in adiponectin levels in various degrees of COPD obstruction. Table 3 shows that under frail conditions serum adiponectin levels increase. The comparative test showed differences in serum adiponectin levels between degrees of frailty with p=0.015 (p <0.05). Further post-hoc analysis showed significant differences in serum adiponectin levels between frail and prefrail patients, and between robust and frail patients. Furthermore, analysis with Spearman's correlation between serum adiponectin levels and

**Table 1.** General characteristics of the subjects

Characteristics	Total
Age. year (Mean ± SD)	(70.26 ± 7.52)
(Min-Max)	(60 - 84)
Education. n (%)	
No formal education	3 (7.9%)
Elementary	12 (31.6%)
Junior Secondary	7 (18.4%)
Senior Seconday	15 (39.5%)
High Education	1 (2.6%)
Nutritional Status (BMI)	
Low (BMI<18.5)	10 (26.3%)
Normal (BMI 18.5-25.0)	21 (55.3%)
High (BMI>25.0)	7 (18.4%)
Smoking History	
Yes	38 (100%)
No	0
Comorbidities	
Hypertension	4 (10.5%)
Heart disease	1 (2.6%)
Renal disease	0
Liver disease	0
Degree of COPD obstruction	
Mild	16 (42.1%)
Moderate	14 (36.8%)
Severe	8 (21.1%)
Very Severe	0

Table 2. Particular characteristics of the subjects

Frailty components	Frequency	Percent
Fatigue (CESD)		
Yes	23	60.5
No	15	39.5
Weight loss		
Yes	11	28.9
No	27	71.1
PASE		
Yes	10	26.3
No	28	73.7
Slowness (*Walking*)		
Yes	11	28.9
No	27	71.1
Muscular weakness (*Handgrip*)		
Yes	0	0.0
No	38	100.0
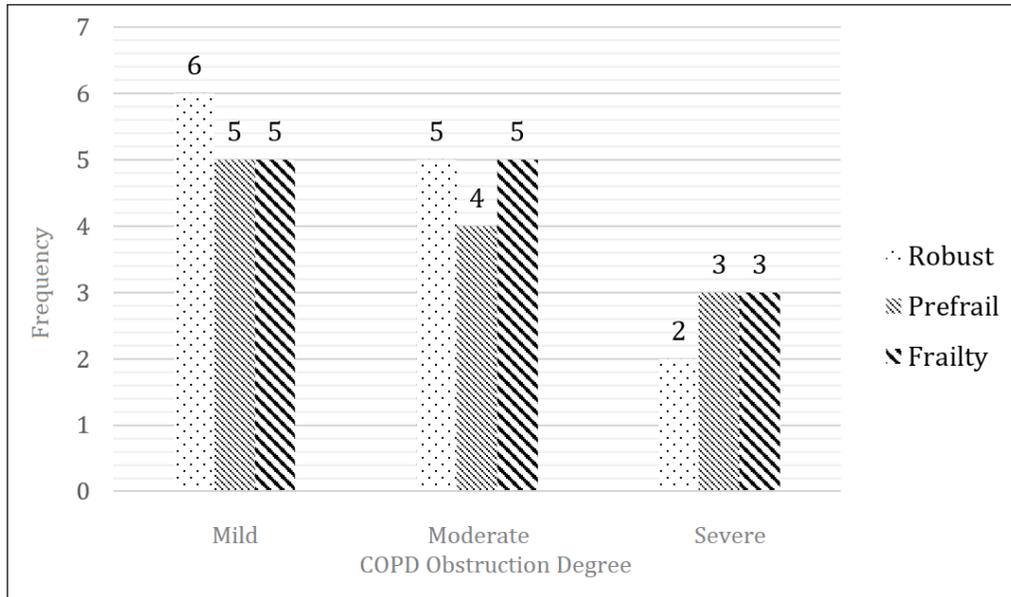
Figure 1. Relationship between the degree of COPD obstruction and frailty frequency.
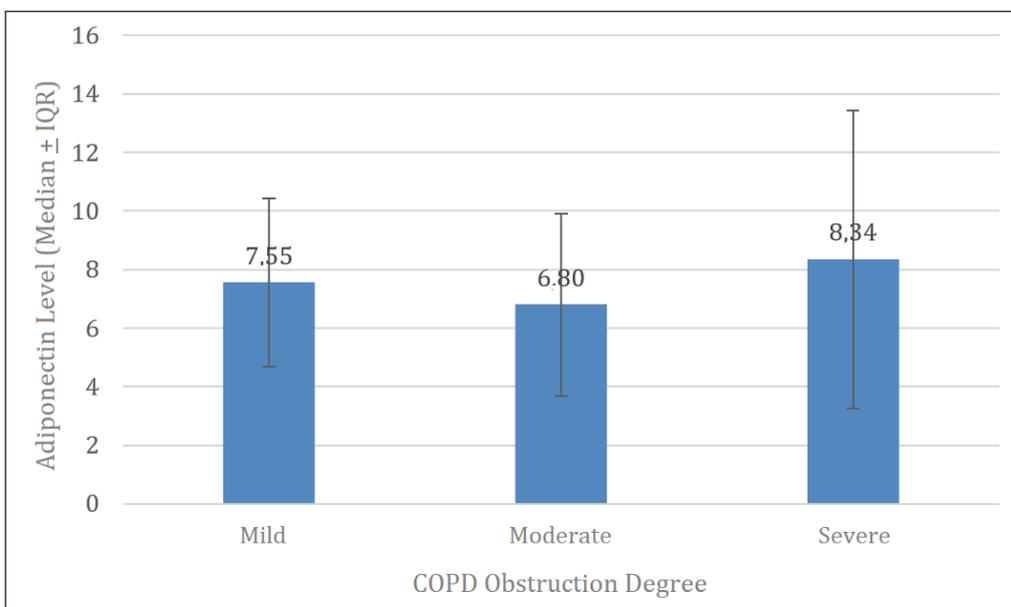
Figure 2. Relationship between the degree of COPD obstruction and adiponectin levels

Table 3. Adiponectin levels at various frailty levels

Degree of Frailty	n	Adiponectin Level					p
		Mean	SD	Median	Minimum	Maximum	
Robust	13	6.84	2.66	5.94[a]	3.68	11.59	
Prefrail	12	6.58	4.27	5.30[a]	2.70	18.31	0.015*
Frail	13	11.62	4.90	11.36[b]	2.97	17.56	

frailty degrees showed Spearman's correlation coefficient rs=0.368 with p=0.023 (p <0.05), showing the relationship between serum adiponectin levels and frailty degrees. The analysis showed that the higher the degree of frailty, the higher the adiponectin level.

Characteristics of the Subjects

This study was conducted to determine the relationship between serum adiponectin levels and degrees of frailty in COPD patients from mild (GOLD 1) to very severe (GOLD 4) obstruction non-exacerbations with age limited to ≥ 60 years. In this study, the mean age was 70.26 + 7.52 years with an age range between 60-84 years. According to Fried frailty phenotype/CHS system as many as 13 (34.2%) of the total 38 samples included in the robust group, 12 (31.6%) in the prefrail group, and 13 (34.2%) in the frail group. Based on Fried's phenotype criteria and their various modified versions, the prevalence of frailty in adult populations aged 65 years or older in the United States ranges from 7% to 12% and increases according to the age group of 3.9% in 65 to 74 the age group, and increased to reach 25% in age group above 85 years.[21] This is similar to the findings in this study, that the robust group was found in the age range of 60-69 years while most of the frail group were over the age of 70 years.

Subjects in this study were all male, although the authors did not limit only one sex. In this study, 21 patients (55.3%) had normal BMI, 10 patients (26.3%) with low BMI, and 7 patients (18.4%) with high BMI. A study conducted by Vestbo et al in 2008 also reported that 96.9% of the COPD population had a normal or high BMI. We also find similar findings. A population-based epidemiological study conducted by de Oca who examined BMI in COPD patients conducted in 5 cities in Latin America showed that most Asian ethnicities had normal BMI, compared with less and more BMI.

In this study the most comorbidity was hypertension, which was as much as 10.5%, followed by heart disease of 2.6%. Other comorbidities such as diabetes mellitus were excluded in this study because diabetes mellitus can affect the results of adiponectin levels. In diabetes mellitus the level of adiponectin is low. In this study, various degrees of frailty were found in various degrees of COPD, it was apparent that that prefrail and frail conditions were more common in COPD subjects (Table 2)

Determining the Degree of Frailty in Elderly COPD Patients

In this study, COPD subjects were obtained with various degrees of frailty, both in COPD with mild, moderate and severe obstruction. This shows that the higher the degree of obstruction, the higher the increase of prefrail and frail conditions. In a study conducted by Lahouse in 2014 on the risk of frailty in elderly, as many as 28.8% of COPD patients were found to be frail, 16.4% prefrail and 14.1% robust.[22] This was different from this study's finding, where frail and robust had the same prevalence. This could be caused by age. The robust patients were mostly in the age range of 60 years while the frail ones were mostly in the age range of 70 years. In a study conducted by Lahouse, the average age was 70 years. If the degree of obstruction was categorized based on GOLD classification, out of 402 COPD subjects, patients with mild obstruction were 200 subjects (49.8%), moderate obstruction 174 subjects (43.3%) and severe obstruction 28 subjects (7,0%). In this study, the prevalence of frailty was strongly related to the severity of COPD, according to the degree of obstruction based on GOLD classification. The higher the degree of COPD obstruction, the frailer condition obtained, as compared to robust and prefrail conditions.[22]

Measuring Adiponectin Level in Elderly COPD Patients

This study found elevated levels of adiponectin in COPD patients, with a median of 7.55 µg/ml in mild obstruction, 6.80 µg/ml in moderate obstruction, and 8.34 µg/ml in severe obstruction. The highest increase was found in COPD with severe obstruction. Chan, who examined serum levels of adiponectin in COPD patients in 2010, found that COPD subjects who smoked had significantly higher levels of adiponectin, IL-6 and CRP than healthy smokers and nonsmokers. This study found that the higher the degree of COPD, the higher the serum adiponectin level. Serum adiponectin, IL-6 and CRP levels were negatively correlated with FEV1 (% predicted) in COPD patients and healthy smokers.[23] Similar

to this study and Chan's study, Tomoda et al. examined the levels of adiponectin in COPD with low and normal body weight, also found increased levels of adiponectin in COPD subjects.[6]

Relationship between Serum Adiponectin Levels and Degree of Frailty in Elderly COPD Patients

In this study, the median serum adiponectin levels in the robust, prefrail, and frailty groups were 5.9 µg/ml (3.68-11.59), 2.70 µg/ml (2.70-18,31), and 11.36 µg/ml (2.97-17.56) respectively. These results indicated that higher serum adiponectin levels are found at a higher degree of frailty. This study also found differences in adiponectin level between degrees of frailty and, in addition, also found a relationship between levels of adiponectin with degrees of frailty with Spearman's correlation coefficient of 0.368 and p=0.023 (p <0.05), showing a relationship between adiponectin levels and the degree of frailty. The analysis showed that the higher the level of adiponectin, the higher the degree of frailty.

In a study conducted by Tsai, who examined the relationship between adiponectin levels and frailty components, 168 subjects were found to be 65-90 years old, and 83 (49.4%) were male. Serum adiponectin levels differed significantly between the three subgroups (p=0.012). The results of the study showed that plasma adiponectin levels were positively related to an increase in frailty components in older men.[10] In contrast to our study, the subjects in Tsai's study were elderly (>60 years), and Tsai's study as well as this study showed an increase in adiponectin levels. This indicates that in the elderly the adiponectin level is increasing.

This study did not find female respondents because female COPD sufferers were rarely found. However, the data in this study, as those of Tsai's and Huang's findings showed that sex was an important factor that could have affected not only blood adiponectin levels, but also the severity of frailty.[24,25]

CONCLUSIONS

Serum adiponectin level in all subjects was found to increase with median in robust, prefrail, and frailty groups. The highest increase was found in severe degree COPD. A weak positive relationship was found between adiponectin level and the degree of frailty.

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