Relationship of adiponectin levels with the severity of chronic obstructive pulmonary disease

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Key words: COPD, adiponectin, adipokines.

Contributions: RS, writing, data collection, and drafting of the article; MI, BN, ID, SN, EA, provided direction and acted as supervisors to improve the article. This article has been read and approved by all authors.

Conflict of interest: the authors declare that they have no competing interests

Ethics approval and consent to participate: all study's actions were approved by the parents, guardians, and patients via an informed consent form after they were informed of the planned course of action. The research was deemed to comply with ethical standards by the Biomedical Research Ethics Commission on Humans, Faculty of Medicine, Hasanuddin University (number: 630/UN4.6.4.5.31/PP36/2024).

Informed consent: before conducting the examinations required in this study, each research subject must sign an informed consent if they agree to participate in this study, and without coercion.

Patient consent for publication: this research does not contain patient identities openly, so it does not require patient consent for publication.

Availability of data and materials: not applicable.

Funding: this study was not supported by any sponsor or funder.

Received: 15 April 2025.
Accepted: 4 May 2025.

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Licensee PAGEPress, Italy
Italian Journal of Medicine 2025; 19:2015
doi:10.4081/itjm.2025.2015

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation and tissue damage. Adipose tissue has been identified as a contributing factor to systemic inflammation in COPD. Adiponectin is present in the airway epithelial cells and bronchoalveolar lavage fluid of patients with COPD. This suggests that adiponectin and COPD patients are related. This study aims to determine the relationship between adiponectin levels and the severity of COPD. Patients with COPD who are registered at Hasanuddin University Hospital and who fit the study's criteria served as the subjects of this cross-sectional study. The patients who had other chronic conditions were excluded. Every patient had their adiponectin levels measured. Based on the ABE group, the severity of COPD was evaluated. Version 29.0 of SPSS was used. A total of 88 subjects were included, with 12 (13.6%) women and 76 (86.4%) men. The mean age was 64.29±9.50 years. The mean adiponectin level was 33.57±14.61. Adiponectin levels were significantly correlated with the severity of COPD (p=0.001). In conclusion, the severity of COPD decreases with increasing adiponectin levels.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of illness and mortality worldwide. From 1990 to 2013, COPD climbed to the eighth or fifth most common cause of disease burden worldwide, according to the Global Burden of Disease survey. In 2016, an estimated 251 million people suffered from COPD, according to the World Health Organization in 2017.[1,2] In Indonesia, the prevalence of COPD is 3.7%. Morbidity and mortality have been linked to COPD, which puts a heavy strain on healthcare facilities, adds to the demand on resources, and raises the cost of continuing medical care. As a result, it must be resolved right away.[3]

Through the release of bioactive hormones called adipokines, which act as mediators in the control of inflammatory and metabolic processes, adipose tissue has been implicated in systemic inflammation in COPD.[3,4] Adipocytes are the main source of the cytokine adiponectin (APN).[4] In the last few years, APN has been found to control COPD inflammation by either autocrine or paracrine pathways. Increasing evidence suggests that APN is closely associated with COPD.[5] According to a study by Nigro *et al*. (2023), APN levels were higher in COPD patients than in healthy

controls. In comparison to healthy controls, COPD patients had considerably greater expression levels of interleukin (IL)-2, IL-4, and IL-8, interferon (IFN)-γ, and granulocyte-macrophage colony-stimulating factor. Conversely, IL-10 expression levels were lower in COPD patients than in healthy controls.[3]

By decreasing inflammatory cytokines and triggering anti-inflammatory cytokines by activating all receptors, APN has anti-inflammatory effects. Nuclear factor-κβ (NF-κB) signaling is inhibited *via* the c-cyclic adenosine monophosphate protein kinase A-dependent pathway, and inflammatory cells are directly affected by the inhibition of IL-6 production, which is accompanied by the induction of the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist. Its actions also include preventing the cytokine tumor necrosis factor-α (TNF-α), which promotes inflammation, from being produced. There is ongoing discussion on the precise mechanism by which APN contributes to inflammation in COPD.[6]

Although APN has two roles in the development and course of COPD, its relationship to the disease has not been thoroughly studied.[4] This study aims to confirm this relationship by analyzing the relationship between APN levels and COPD severity.

Materials and Methods

Research design

This study used an observational analytical design with a cross-sectional approach. This study was conducted at the Hasanuddin University (UNHAS) Education Network Hospital.

Research subject

The population of this study consisted of all the patients who had been diagnosed with COPD at the UNHAS Teaching Network Hospital. The inclusion criteria for this study were patients aged ≥40 years, diagnosed with COPD, and willing to sign an informed consent form after being given a complete explanation of the research procedure. COPD patients who suffered from other chronic diseases such as pulmonary tuberculosis, asthma, type 2 diabetes mellitus, hypertension, coronary heart disease, heart failure, kidney failure, and malignancy were excluded from this study. We excluded hypertension and coronary heart disease because they can increase APN levels, which can bias the results. Children were excluded because COPD mostly occurs in people aged ≥40 years. The sampling technique used was consecutive sampling.

Research methods

After obtaining research ethics approval and signed informed consent, the collection of research subjects was carried out. APN examination was carried out on all research subjects. After obtaining the research subjects, APN levels were immediately measured by taking a sample of the patient's venous blood and examining the APN using the enzyme-linked immunosorbent assay method. After all the data is collected, data analysis will be carried out.

Definition

Active smokers are assessed using the Brinkman Index (BI) category: the number of cigarettes per day multiplied by the length of smoking in years, divided into three groups, namely BI for light smokers ≤200, BI for moderate smokers if 201-600, and BI for heavy smokers if >600. Nutritional status is assessed using body mass index: i) underweight <18.5 kg/m^2; ii) normoweight 18.5-22.9 kg/m^2; iii) overweight 23.0-24.9 kg/m^2; iv) obesity ≥25.0 kg/m^2.

Data analysis

SPSS (Statistical Package for Social Science) software version 29 (IBM, Armonk, NY, USA) is used for data analysis. Both descriptive and analytical analyses were performed on the data. The data analysis used was univariate and bivariate.

Univariate analysis: this data is presented through a frequency table to determine the characteristics of the data distribution.

Bivariate analysis: before the bivariate analysis was conducted, a normality test was performed on the APN level variable using the Shapiro-Wilk test. If the data is normally distributed, the Kruskal-Wallis test is used to assess the relationship between APN levels and COPD severity; however, if it is not normally distributed, the Mann-Whitney test is used.

The statistical confidence interval of this study is 95%. If $p<0.05$, then it is considered significant.

Results

Basic characteristics of research subjects

A total of 88 individuals with a diagnosis of COPD participated in this study. Males were more than females (86.4% *vs.* 13.6%). A total of 27 people (30.7%) were aged <60 years, and 61 (69.3%) were aged ≥60. Normal nutritional status was the most common in this study (46.6%). Based on smoking status, 19 people (21.6%) did not smoke, 5 people (5.7%) were light smokers, 25 people (28.4%) were moderate smokers, and 39 people (44.3%) were heavy smokers. Based on the ABE group, 32 people (36.4%) group A, 33 people (37.5%) group B, and 23 people (26.1%) group E. Based on the Modified Medical Research Council, the severity of COPD consists of 4 people (4.5%) belonged to grade 0, 34 people (38.6%) to grade 1, 38 people (43.2%) to grade 2, and 12 people (13.6%) to grade 3. Based on therapy compliance, 36 people (40.9%) were compliant with treatment, and 52 people (59.1%) were non-compliant with treatment. Based on the Global Initiative for Chronic Obstructive Lung Disease, the severity of COPD consists of 5 people (5.7%) had mild obstruction, 23 people (26.1%) had moderate obstruction, 35 people (39.8%) had severe obstruction, and 25 people (28.4%) had very severe obstruction. The mean forced expiratory volume in 1 second (FEV1) in this study was 42.95±18.33, and the mean FEV1/forced vital capacity was 95.24±27.27. The mean APN level in COPD patients was 33.57±14.61 (Table 1).

Relationship between adiponectin levels and severity of chronic obstructive pulmonary disease

The relationship between APN levels and COPD severity is presented in Table 2. Group A had a high mean APN of 38.12±11.36, compared to group B of 35.77±18.09, and group E of 24.10±7.38. There was a significant relationship between APN levels and COPD severity (p=0.001).

Relationship between adiponectin levels and chronic obstructive pulmonary disease obstruction levels

Based on the degree of obstruction, subjects with mild obstruction had a mean APN of 23.81±12.27; 32.14±10.47 in moderate obstruction; 33.79±17.45 in severe obstruction; and 36.54±13.63 in very severe obstruction (Table 3). There was no significant relationship between APN levels and the level of COPD obstruction based on GOLD (p=0.105).

Relationship between gender, age, nutritional status, smoking status, and therapy compliance with chronic obstructive pulmonary disease severity

This study also assessed the relationship between gender, age, nutritional status, smoking status, and therapy compliance with COPD severity. Based on gender, group A consisted of 6 (50.0%) women and 26 (34.2%) men, group B consisted of 2 (6.1%) women and 31 (30.8%) men, and group E consisted of 4 (33.3%) women and 19 (25.0%) men.There was no significant relationship between gender and COPD severity based on the ABE group (p=0.277). Based on age, group A consisted of 12 (44.4%) aged <60 years and 20 (22.2%) aged ≥60 years. Group B consisted of 10 (37.0%) aged <60 years and 23 (37.7%) aged ≥60. Group E consisted of 5 (18.5%) aged <60 years and 18 (29.5%) aged ≥60. There was no significant relationship between age and COPD severity based on the ABE group (p=0.457) (Table 4). Based on nutritional sta-

Table 1. Characteristics of the research subjects.

Variable	Frequency, n or mean±SD	Percentage
Gender		
Women	12	13.6
Men	76	86.4
Age		
<60 years	27	30.7
≥60 years	61	69.3
Nutritional status		
Underweight	32	36.4
Normoweight	41	46.6
Overweight	12	13.6
Obesity	3	3.4
Smoking status		
Not smoking	19	21.6
Mild smoker	5	5.7
Moderate smoker	25	28.4
Severe smoker	39	44.3
ABE group		
A	32	36.4
B	33	37.5
E	23	26.1
MMRC		
Degree 0	4	4.5
Degree 1	34	38.6
Degree 2	38	43.2
Therapy compliance		
Obedient	36	40.9
Not obey	52	59.1
GOLD category		
Mild	5	5.7
Moderate	23	26.1
Severe	35	39.8
Very severe	25	28.4
FEV1	42.95±18.33	
FEV1/FVC	95.24±27.27	
Adiponectin levels	33.57±14.61	

SD, standard deviation; MMRC, Modified Medical Research Council; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

tus, group A consisted of 5 (15.6%) underweight people, 19 (46.3%) normoweight people, and 6 (50.0%) overweight people. Group B consisted of 10 (31.3%) underweight people, 16 (39.0%) normoweight people, 6 (50.0%) overweight people, and 1 (33.3%) obese individual. Group E consisted of 17 (53.1%) underweight people and 6 (14.6%) normoweight people. There was a significant relationship between nutritional status and the severity of COPD based on the ABE group ($p \leq 0.001$). In group A, 11 people (57.9%) were non-smokers, 10 people (40%) were moderate smokers, and 11 people (28.2%) were heavy smokers. In group B, 3 people (15.8%) were non-smokers, 5 people (100%) were light smokers, 7 people (28%) were moderate smokers, and 18 people (46.2%) were heavy smokers. In group E, 5 people (26.3%) were non-smokers, 8 people (32%) were moderate smokers, and 10 people (25.6%) were heavy smokers. There was no significant relationship between smoking status and COPD severity

Table 2. Relationship between adiponectin levels and severity of chronic obstructive pulmonary disease.

Variable ABE group	Frequency (n)	Adiponectin	p
A	32	38.12±11.36	0.001*
B	33	35.77±18.09	
E	23	24.10±7.38	
A+B	-	36.93±15.09	<0.001#
E	23	24.10±7.38	
A+E	-	32.26±12.04	
B	33	35.77±18.09	0.472#
B+E	-	30.98±15.68	
A	32	38.12±11.36	<0.001#

*Kruskal-Wallis; #Mann-Whitney.

Table 3. Relationship between adiponectin levels and chronic obstructive pulmonary disease obstruction levels.

Variable GOLD	Frequency (n)	Adiponectin	p
Mild	5	23.81±12.27	0.105#
Moderate	23	32.14±10.47	
Severe	35	33.79±17.45	
Very severe	25	36.54±13.63	

#Kruskal-Wallis; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 4. Relationship between gender, age, nutritional status, smoking status, and therapy compliance with chronic obstructive pulmonary disease severity.

Variable	Group A, n (%)	Group B, n (%)	Group E, n (%)	p
Gender				0.277#
Women	6 (50.0)	2 (6.1)	4 (33.3)	
Men	26 (34.2)	31 (30.8)	19 (25.0)	
Age				0.457##
<60 years	12 (44.4)	10 (37)	45(18.5)	
≥60 years	20 (32.8)	23 (37.7)	18 (29.5)	
Nutritional status				<0.001##
Underweight	5 (15.6)	10 (31.3)	17 (53.1)	
Normoweight	19 (46.3)	16 (39.0)	6 (14.6)	
Overweight	6 (50.0)	6 (50.0)	0 (0)	
Obesity	2 (66.7)	1 (33.3)	0 (0)	
Smoking status				0.179#
Not smoking	11 (57.9)	3 (15.8)	5 (26.3)	
Mild smoker	0 (0)	5 (100)	0 (0)	
Moderate smoker	10 (40)	7 (28)	8 (32)	
Severe smoker	11 (28.2)	18 (46.2)	10 (25.6)	
Therapy compliance				0.126##
Obedient	11 (30.6)	18 (50.0)	7 (19.4)	
Not obey	21 (40.4)	15 (28.8)	16 (30.8)	

#Kruskal-Wallis; ##Chi-square.

(p=0.179). Based on therapy compliance, group A consisted of 11 (30.6%) compliant and 21 (40.4%) non-compliant, group B consisted of 18 (50.0%) compliant and 15 (28.8%) non-compliant, and group E consisted of 7 (19.4%) compliant and 16 (30.8%) non-compliant. There was no significant relationship between therapy compliance and COPD severity based on the ABE group (p=0.126) (Table 4).

Discussion

In this study, men were more prevalent than women. Smoking is more common in men than in women, which causes an increased risk of COPD in men.[7] Age ≥60 years is more than age <60 years. In line with Cosio *et al*. (2022), the mean age of COPD sufferers in the study was 67.8 years.[8] As people age, their lung function capacity may decline, making them more vulnerable to lung disease and more often engage in unhealthy behaviors.[9] Up to 44.3% of the participants in this study had COPD and were heavy smokers. Protease, anti-protease, oxidant-antioxidant, and aberrant repair processes are all part of the pathophysiology of smoking-related COPD.[10]

The results of this study indicate that there is a significant relationship between APN groups and the severity of COPD (p=0.001). The mean APN levels were higher in group A and lower in group E. Until now, there has been no study analyzing the relationship between APN levels and the severity of COPD based on the ABE group. However, it is consistent with Daniele *et al*. (2012) that APN functions as an anti-inflammatory factor that protects against the pathophysiology of COPD.[11] Although the study did not describe a direct relationship between APN levels and the severity of COPD, it can support the results of this study with the anti-inflammatory effect of APN levels, which can reduce the severity of COPD.

These findings contradict those of Jaswal *et al*. (2018): APN levels were higher in the COPD group than in the control group, and the levels of APN with the severity of the disease reached 16.10±4.97 ng/mL in the acute exacerbation of COPD group and 11.43±4.22 ng/mL in the COPD group.[12] Lin *et al*. (2020) also proved that serum APN levels were greater in individuals experiencing an acute exacerbation of COPD compared to those with stable COPD.[13] There are differences in characteristics and measurement definitions between this study and the studies of Jaswal *et al.* (2018) and Lin *et al.* (2020). Both studies assessed the severity of COPD based on the GOLD category. This study assessed the severity of COPD based on the ABE group.

APN is believed to play a role in several metabolic functions, including inflammation, lipid and glucose metabolism, insulin resistance, and immunology. It circulates in complexes with varying molecular weights and is released in serum. AdipoR1, AdipoR2, and T-cadherin, which are found on epithelial and endothelial lung cells, indicate a functional involvement in lung physiology.[12] NF-κB was inhibited by APPL1-mediated APN signaling. To keep NF-κB in the cytosol, inactivated NF-κB binds to its inhibitory protein, IκB. After IκB is phosphorylated and partially degraded, NF-κB is activated and moved into the nucleus, where it promotes the expression of many genes; finally, the synthesis of pro-inflammatory cytokines decreased.[14,15] APN's ability is to inhibit proinflammatory cytokines and induce IL-10. APN promotes the fast production of TNF-α and IL-10, which in turn creates a condition of tolerance to further lipopolysaccharide stimulation. APN stimulates NF-κB translational activity, IL-6 synthesis and expression, and *MCP-1* expression in adipocytes exposed to lipopolysaccharide. APN may be a regulator of local inflammation in adipose tissue because it increases the expression of peroxisome proliferator-activated receptor γ2, which decreases NF-κB's DNA binding.[15]

In addition, APN can bind to APN receptors on airway epithelial cells and cause increased IL-8 expression. Finally, neutrophils migrate and accumulate in the airways, thereby mediating inflammatory reactions. Furthermore, APN mimics the M1 proinflammatory response but does not induce alternative macrophage activation (M2). APN enhances Th2 differentiation, causing mRNA expression and protein release of inflammatory molecules, including IFN-γ and IL-6.[16,17] The potential relationship between adipose tissue and COPD inflammation/metabolic disorders may be related to the endocrine function of adipose tissue, thereby increasing adipokine secretion.[3] In addition to assessing the relationship between APN levels and COPD severity, this study also showed that there was no significant relationship between APN levels and the degree of COPD obstruction based on GOLD. However, this study showed that mild degrees had the lowest average APN levels and increased with increasing COPD severity.

There are several variables that can affect the severity of COPD. This study shows that nutritional status can affect the severity of COPD. Ariyani *et al.* (2013) showed a relationship between nutritional status and lung function. Normal nutritional status was more common in the normal lung function group, while abnormal nutritional status was more common in the abnormal lung function group (p=0.030). COPD often causes malnutrition, which is caused by the need for additional energy due to increased respiratory muscle work, due to chronic hypoxemia and hypercapnia, which cause hypermetabolism.[18,19] This study did not find any significant relationship between gender, age, smoking status, and therapy compliance with COPD severity. Changes in habits between genders may be the cause of the insignificant results of this study. This study also only included people aged 40 years and over, so it cannot be compared with younger ages. Other factors are a history of recurrent respiratory infections, exposure to pollution smoke, and a history of smoking.[20] Also, in this study, the data distribution is not homogeneous.

This study has limitations in that it did not assess confounding factors such as comorbidities, which may affect APN levels, so that it can provide more information on the relationship between APN levels and COPD severity. In addition, the design of this study used a cross-sectional study that assessed all variables at one time, so it was less able to describe a clear relationship. However, this study can still explain the relationship between APN levels and COPD severity.

Conclusions

Based on the ABE group, COPD severity was significantly correlated with APN levels.

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