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Effect of *Ophiocephalus striatus* Extract on the Levels of TNF-α, CRP, Leptin, Adiponectin, and COPD Assessment Test (CAT) Score in Stable COPD Patients with Muscle Wasting

Ophiocephalus striatus Ekstresinin Kas Erimesi Olan Stabil Kronik Obstrüktif Akciğer Hastalarında TNF-alfa, CRP, Leptin ve Adiponektin Düzeylerine Olan Etkisi

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Abstract

Introduction: Muscle wasting is an extrapulmonary manifestation that occurs in 20–40% of patients with Chronic Obstructive Pulmonary Disease (COPD). The purpose of this study is to confirm whether nutrition support can improve inflammation (measured by levels of TNF-α, CRP, leptin, and adiponectin), muscle wasting, and quality of life of COPD patients with muscle wasting.

Material and Methods: The study design was a clinical pre-and post-auto-control quasi-experimental, conducted with a sample of stable COPD patients with comorbid muscle wasting. Muscle wasting was diagnosed through examination of the Bioelectrical Impedance Analysis (BIA). Levels of leptin and adiponectin were measured using the Enzyme-linked immunosorbent assay (ELISA) method, and quality of life was assessed using COPD Assessment Test (CAT) score. BIA, TNF-α, CRP, leptin, adiponectin, and CAT were measured in 32 COPD patients with muscle wasting, before and after 12 weeks supplementation with *Ophiocephalus striatus* extract, 3x1000 mg/day.

Results: There was a significant increase in body-mass index (BMI) (p=0.046), no significant increase in Fat-free mass index (FFMI) (p=0506), no significant decrease in TNF-α and CRP, a significant decrease in leptin levels (p <0.001), a significant increase in adiponectin levels (p=0.048), and a significant improvement in quality of life (score CAT) (p <0.001) after administration of *Ophiocephalus striatus* extract for 12 weeks.

Conclusion: Supplementation with *Ophiocephalus striatus* extract for 12 weeks can improve BMI, decrease levels of TNF-α, CRP, and leptin, increase the level of adiponectin, and result in improvement in the quality of life of stable COPD patients with muscle wasting.

Keywords: Adiponectin, Chronic Obstructive Pulmonary Disease, Leptin, Muscle wasting, *Ophiocephalus striatus* extract

Öz

Giriş: Kronik Obstrüktif Akciğer Hastalığı (KOAH) bulunan olguların %20-40'ında kas erimesi bulunmaktadır. Bu çalışmanın amacı, KOAH'lı hastalarda yapılan beslenme desteğinin, (TNF-α, CRP, leptin ve adiponektin ile ölçülebilen) yangıyı azaltıp azaltmadığını ve kas erimesi ile hayat kalitesine olan etkisini araştırmaktır.

Gereçler ve Yöntemler: Çalışma, kas erimesi olan ve KOAH'ı bulunan hastalarda önce ve sonra kontrollü yarı deneysel bir klinik çalışma olarak tasarlandı. Kas erimesi, Bioelektrik empedans analizi ile (BEA) ölçüldü. eptin ve adiponektin düzeyleri ELISA metodu ile, hayat kalitesi ise, KOAH Değerlendirme Testi (KDT) ile saptandı. BEA, TNF-α, CRP, leptin adiponektin ve KDT ölçümleri, 32 hastada, 12 hafta boyunca günde 3 kez 1000mg Ophiocephalus striatus ekstresi verilmeden ve verildikten sonra ölçüldü.

Bulgular: On iki hafta boyunca Ophiocephalus striatus ekstresi verildikten sonra vücud kitle indeksinde (p=0.046) anlamlı bir artış olur iken, yağsız kitle indeksi(YKİ)'nde(p=0.506), TNF-α, CRP düzeylerinde ise belirgin bir artış saptanmadı. Hayat kalitesi ölçümlerinde (KDT) ise anlamlı bir artış (p<0.001) bulundu.

Sonuç: On iki hafta boyunca Ophiocephalus striatus ekstresi verilmesi, VKİ'ni artırmakta, TNF-α, CRP, leptin düzeylerini düşürmekte adiponektin düzeyini artırarak, kas erimesi olan KOAH hastalarında hayat kalitesini yükseltmektedir.

Anahtar Kelimeler: Adiponektin, Kronik obstrüktif akciğer hastalığı (KOAH), leptin, kas erimesi, Ophiocephalus striatus ekstresi

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Introduction

One of the main problems faced by Chronic Obstructive Pulmonary Disease (COPD) patients with muscle wasting is a significant decrease in the structure and function of skeletal muscles. This systemic manifestation has a significant influence on the tolerance and life quality of the patient and is also associated with the increased mortality in COPD patients.

Leptin is a hormone secreted by adipocytes, emerging as a pleiotropic cytokine, involved in the activation and recruitment of inflammatory cells. Leptin level is positively correlated with inflammatory markers such as C-reactive protein (CRP) and Tumor Necrosis Factor Alpha (TNF-α). This suggests that leptin is involved in the inflammatory response in COPD.[1,2]

Adiponectin has an anti-inflammatory effect and plays an important role in energy homeostasis, glucose regulation, and lipid metabolism. It is synthesized and secreted by adipose tissue. A previous study indicated that adiponectin exerts its anti-inflammatory properties by inhibiting pro-inflammatory mediators (TNF-α, IL-6, ICAM-1 endothelial adhesion molecules, and nuclear factor-κβ) and promoting anti-inflammatory mediators (IL-10 and receptor antagonist IL-1).[3]

The high prevalence of muscle wasting in COPD patients requires preventative and curative actions. Nutritional therapy in COPD patients is expected to provide an enhancement in body functions, one of which is an improvement in muscle strength.

Catfish extract (*Ophiocephalus striatus*) contains a high amount protein and albumin, which are needed by the body. The relationship between various inflammatory markers in the circulatory system and loss of muscle mass in COPD is still under study. In addition, it is important to understand the assessment of muscle mass and systemic effects. This would allow the development of new strategies that could be considered as part of the therapy for COPD and could contribute to the evaluation of management strategies so as to deliver a better therapeutic result.[4]

Material and Methods

This study was conducted between January and December 2015. The study design was a clinical pre-and post-auto-control, quasi-experimental design among stable COPD patients with comorbid muscle wasting. This study aimed to explore the effects of catfish extract (Ophiocephalus striatus; Vipalbumin®) in patients with comorbid muscle wasting, in relation to the levels of TNF-α, CRP, leptin, adiponectin, and COPD Assessment Test score (CAT score).

The sample comprised stable COPD patients with muscle wasting who were taking medication and were patients of the Pulmonary Outpatient Clinic of Dr. Saiful Anwar Hospital. Thirty-two patients who met the inclusion and exclusion criteria were chosen. Each procedure was approved by the ethics committee, and each patient volunteered to participate in the study and signed the informed consent.

The inclusion criteria were: male patients with comorbid muscle wasting, aged 40 to 65 years, meeting the criteria of The Global Initiative for Obstructive Lung Disease[4], and taking maintenance therapy with standard COPD medication. Patients with other comorbid diseases, such as diabetes, chronic renal failure, chronic heart failure, malignancy, liver disorder, other systemic chronic diseases, stroke, and thyroid dysfunction, were excluded. Patients who took other nutritional therapy or systemic steroid therapy, and patients who had exacerbations in the last three months, were also excluded. Patients who had exacerbations during the study or who did not come back for therapy were declared as drop-outs.

Comorbidity of muscle wasting was diagnosed according to the Fat-Free Mass Index (FFMI) <16 kg/m^2. This was measured using bioelectrical impedance (BIA) Omron Karada Scan HBF-375.500 mg Vipalbumin®, a high protein nutritional supplement produced by PT. Royal Medika, was consumed three times per day (in the form of two capsules) for 12 weeks. Patients were assessed before and after Vipalbumin® supplementation. The assessments included body composition, CAT score, TNF-α level (using ELISA legend MaxTM Human TNF-α pre-coated plates), CRP (using Elisa Kit The EiAsyTM Way), leptin level (using ELISA EiAsy Leptin Test Kit), and adiponectin (using ELISA LEGEND MAX Human Adiponectin precoated ELISA kit).

Results

Patients were aged 46 to 65 years. The average age was 62.7±4 years. Education levels varied from elementary

Table 1. Sociodemographic characteristics of research subjects

Characteristics		Number	Percentage (%)
Age (years)	40–45	1	3.1
	46–50	0	0
	51–55	0	0
	56–60	2	6.3
	61–65	29	90.6
Education Levels	Elementary School	6	18.8
	Junior High School	2	6.3
	Senior High School	21	65.6
	Diploma	1	3.1
	Bachelor	2	6.3
Occupation	Unemployed	2	6.3
	Entrepreneur	7	21.9
	Private employees	2	6.3
	Pensionary	17	53.1
	Farmer	3	9.4
	Driver	1	3.1
Payment	General	1	3.1
	BPJS*	31	96.9
Income	<Rp 500.000	1	3.1
	Rp 500.000–1.000.000	7	21.9
	Rp 1.000.000–2.000.000	20	62.5
	>Rp 2.000.000	4	12.5

* Badan Penyelenggara Jaminan Sosial: the national health care security in Indonesia

Table 2. Clinical characteristics of research subjects

Characteristics		Number	Percentage (%)
Brinkman Index	Mild (1–50)	1	3.1
	Medium (51–100)	1	3.1
	Heavy (>100)	30	93.8
Cigarette smoking (pack.years)	Mild (<10)	4	12.5
	Heavy (>10)	28	87.5
Body Mass Index (kg/m^2)	<18.5	13	40.6
	18.5–24.9	16	50.0
	25–29.9	3	9.4
COPD stages	GOLD I	2	6.3
	GOLD II	14	43.8
	GOLD III	12	37.5
	GOLD IV	4	12.5
CAT	<10	5	15.6
	≥10	27	84.4
mMRC*	0–1	7	21.9
	≥2	25	78.1
Exacerbation per year	0–1	22	68.8
	≥2	10	31.3
COPD population	A	3	9.4
	B	9	28.1
	C	2	6.3
	D	18	56.3
Comorbid other than *muscle wasting*	Presence	2	6.3
	Absence	30	93.8

* modified Medical Research Council , COPD: Chronic obstructive pulmonary disease, CAT:COPD Assessment test

to graduate school. The majority of participants had completed senior high school (62.5%; 20 people). The most commonly reported occupation was pensioner (53.1% ; 17 people). All patients were married and lived with their partner or family (Table 1).

In this study, there was no patient who dropped out and intolerance to Vipalbumin. After the administration of Vipalbumin® for three months, there was an improvement in the FFMI score of the patients (11.9±2.0 to 12.4±2.4) (p=0.057). There was also a percentage increase in Intima Media Thickness (IMT) score after Vipalbumin® administration, for the normal weight and overweight patients (Table 3; p=0.046)).

The mean value of TNF-α levels was 192.0±79.0 pg/mL, and mean CRP was 6.0±1.5 pg/mL, after Vipalbumin (Table 4; p=0.006 and 0.751 respectively). The mean leptin and adiponectin levels before Vipalbumin administration

Table 3. Distribution of research subjects based on Body Mass Index (BMI) before and after Vipalbumin® administration

BMI	Number of subjects			
	Before		After	
	N	%	N	%
<18.5	13	40.6	10	31.3
18.5–24.9	16	50.0	18	56.3
≥25	3	9.4	4	12.5

were 14.0±14.5 ng/mL and 9.0±2.7 ng/mL, respectively, while the mean levels after administration were 8.0±6.0 ng/mL and 11.0±2.3 ng/mL, respectively (Table 4). The analysis showed that there was a significant decrease in leptin level (p<0.001) and a significant increase in adiponectin levels (p=0.048) caused by Vipalbumin® administration.

Table 4. TNF-α, CRP, Leptin Adiponectin levels before and after Vipalbumin® administration (N=32)

Parameter	Mean	Std. Deviation	P
TNF-α Pre pg/mL	194	91	0.906
TNF-α Post pg/mL	192	79	
CRP Pre mg/L	6.30	1.71	0.751
CRP Post mg/L	5.98	1.48	
Leptin Pre ng/mL	14.24	14.48	0.048
Leptin Post ng/mL	8.17	6.89	
Adiponectin Pre ng/mL	9.30	2.71	<0.001
Adiponectin Post ng/mL	11.0	2.3	

Table 5. The result of paired t-test of COPD Assessment Test (CAT)

Parameter	Mean	P
CAT (pre-administration)	18.34±8.03	<0.001
CAT (post-administration)	10.81±7.66	

The relationships between FFMI value changes and the levels of TNF-α and CRP are presented in Table 6. There was a weak positive correlation between FFMI and TNF-α levels as well as between FFMI and CAT measurements. In contrast, there was a weak negative correlation between CRP and FFMI levels that showed differences between pre-and post-administration of catfish extract. However, neither of these correlations were statistically significant.

Table 6. Correlation of FFMI changes with the changes in TNF-α, CRP, and CAT levels

Pearson Correlation	FFMI changes	
	r	P
Change in TNF levels	0.09	0.625
Change in CRP levels	-0.11	0.549
Change in CAT scores	0.011	0.953

The relationships between CAT score and both TNF-α and CRP levels were different before and after supplementation. There was a weak negative correlation between TNF-α levels and CAT scores, while there was a weak positive correlation between CAT scores and CRP levels, after administration of the extract. However, none of these correlations were statistically significant (Table 7).

Table 7. Correlation of TNF-α and CRP level changes with the changes in CAT level

Pearson Correlation	CAT changes	
	r	P
TNF-α changes	-0.303	0.092
CRP changes	0.206	0.257

The relationships between BMI change and leptin, adiponectin, and CAT score are presented in Table 8. BMI change showed a weak negative correlation with both leptin and adiponectin measurements, though this was not statistically significant. In contrast, BMI change demonstrated a weak positive correlation to CAT score without statistical significance. FFMI was negatively correlated with leptin and adiponectin . However, the difference did not not reach the statistical significance (Table 9).

Table 8. Correlation of BMI changes with the changes in Leptin, Adiponectin, and CAT score

Pearson correlation	CAT changes	
	R	P
Change in leptin levels	-0.041	0.822
Change in adiponectin levels	-0.125	0.495
Change in BMI	0.101	0.583

Table 9. Correlation of FFMI changes with the changes in Leptin, Adiponectin, and CAT Level

Pearson correlation	FFMI changes	
	R	P
Change in leptin levels	-0.122	0.506
Change in adiponectin levels	-0.128	0.484
Change in CAT scores	0.11	0.953

Conclusion

The average age of the participants in this study was 62.7 years. This is in accordance with a previous study of Turkish COPD patients with muscle wasting, which had an average age of 62.1 years. Meanwhile, in an English study, the COPD patients had a low average FFMI score, with an average age of 62.1±8.7 years.[5,6] There are several factors that might affect the results of FFMI score in this study, such as the daily intake of each participant, the regularity on consuming the nutrition, and the level of physical activities.

Most of the participants in this study had a normal range BMI score, although there was a tendency for the patients with the highest COPD stages to have the lowest BMI scores. Weight loss can occur in 10–15% of COPD patients in low-medium stages.[7–9] The highest prevalence of obesity was found in mild stage COPD (GOLD I and II) and was rarely found in GOLD IV stage. There is at

least one or more component of the metabolic syndrome in nearly 50% of patients.[10] In the current study, three overweight persons were recorded, two of them were classified as COPD B and one as COPD D. This finding is in accordance with a previous study. Classification as overweight usually occurs in patients with muscle wasting due to a decrease in fat-free mass and an increase in fat mass. Basically, the BMI measurement does not reflect body composition according to the metabolic and functional effects, such as FFMI, which is reduced in patients with muscle wasting.

According to the present study, approximately 84.4% of patients had a CAT score higher than 10 before treatment. This result is predicted to be associated with poor functional status and poor quality of life due to a decrease in the number and function of skeletal muscle.[11]

The results of this study indicated that 9.3% of participants had a comorbidity other than muscle wasting; specifically, comorbid hypertension was common. This finding emphasizes the importance of understanding the comorbidity or multi-comorbidity in COPD patients. This finding is supported by a previous study indicating that 9.7% of COPD patients had one or more comorbidities, and half of these had at least four comorbidities.[12]

The present study reported a change in the average BMI before and after treatment (p=0.046), from 20.0±3.6 kg/m^2 to 21.0±3.5 kg/m^2. This is supported by a previous study that reported the increasing weight of COPD outpatients and found a significant weight increase after the administration of 0.47 g catfish extract for 14 days (three times per day).[13] Similarly, a study from New Delhi also emphasized similar increase in BMI after oral administration of nutrition (Nourish) for three and six weeks.[14] Another study also indicated an increase in average BMI after 12 weeks of nutrition support.[15]

An increase in weight is inferred from BMI changes after the nutrition therapy. The present study showed an increase in average weight, from 51.9 kg to 52.8 kg. This probably resulted from a decrease in leptin levels, which increases appetite and reduces energy expenditure. Vipalbumin® as a protein rich nutritional supplementation affects protein metabolism in peripheral muscles and inhibit the process of skeletal muscle loss then furthermore increase the body fat mass and BMI.

The levels of TNF-α and CRP were increased in the COPD patients with muscle wasting and then showed a decrease after Vipalbumin® administration; though this was not statistically significant. Nutritional support was given in this study using a supplement with a high protein content, containing amino acids, complete vitamins, and minerals. This is consistent with a previous study in Japan, which provided 12 weeks of nutritional support using a high protein supplement with anti-oxidant and anti-inflammatory properties. This study showed significantly reduced levels of inflammatory cytokines such as TNF-α, IL-6, and IL-8, after supplementation. However, this study used a combination of nutritional therapy with a low-intensity physical exercise program.

Leptin is a pleiotropic cytokine involved in the activation and recruitment of inflammatory cells. The detected leptin levels are positively correlated with inflammatory markers such as CRP and TNF-α. This suggests that leptin is involved in the inflammatory response in COPD.[1,2]

Cells exposed to TNF-α and/or IL-1β, which are potent inflammatory cytokines, could reduce their cytotoxic effects through a certain dose of adiponectin.[16] In addition, adiponectin is also capable of improving cell viability and decreasing apoptosis. Previous studies have also found that adiponectin inhibits transactivation of NF-κb and induces anti-inflammatory IL-10 through ERK1/2, as well as AKT through the mediation of AdipoR1.[3,17]

Catfish extract contains natural complex nutrients, such as protein, albumin, vitamins, minerals, fatty acids, and 15 kinds of amino acids, including five essential amino acids. The current study found a significant decrease in leptin levels after administration of catfish extract. Our results indicated a significant increase in adiponectin level after supplementation with catfish extract (p=0.048). The decreasing level of leptin and increasing level of adiponectin are probably due to the anti-inflammatory effect of catfish extract; whereas, a decrease in systemic proinflammatory cytokines (CRP, TNF-α, and IL-6) is positively correlated with a decrease in leptin level in circulation, and an increase in anti-inflammatory cytokines, such as IL-10 and IL-1 antagonist receptors. The mechanisms of the effects of catfish extract on leptin and adiponectin levels are not yet known.

CAT and Force Expiratory Volume in 1 second (FEV1) are useful methods used for assessing therapeutic response

and progression of disease severity. There is a correlation between CAT and FEV1 scores. CAT is thought to be associated with limited oxygen flow and GOLD classification of stable COPD patients. The severity of oxygen flow limitations is reflected in poorer CAT scores. [18,19]

This study demonstrated that the administration of catfish extract as a form of nutritional support provides a significant improvement in CAT. This improvement may be due to an improvement in FEV1 values, as reflected in GOLD stage changes. The increasing CAT score was strongly associated with more nutrition for patients classified as GOLD A or B. This suggests that nutritional therapy is more effective in the early stages of the disease.

The limitation of this study is the absence of control over the physical exercise of participants; physical exercise is a form of non-medical therapy in the multidimensional treatment of COPD with muscle wasting. This resulted in differing results as compared to previous studies that combined nutritional therapy and physical exercise programs.

In this study, it could be concluded that there is a significant decrease in the levels of TNF-α and CRP after Vipalbumin® administration in stable COPD patients with muscle wasting. There was also a decrease in leptin levels, an increase in adiponectin levels, and a significant decrease in CAT score following Vipalbumin® administration. Furthermore, there were no correlations between FFMI and TNF-α, CRP, leptin, or adiponectin whereas there were also no correlations between changes in TNF-α, CRP, leptin, and adiponectin and the CAT scores after administration of Vipalbumin® for 12 weeks. Longer administration of Vipalbumin® may decrease the levels of TNF-α and CRP significantly.

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Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Author Contributions: Concept - DS; Supervision DS; Data Collection and/or Processing - KE, WKSR; Analysis and/or Interpretation - DS, KE, WKSR; Literature Search - KE, WKSR; Writing Manuscript- KE, WKSR; Critical Review -DS.

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