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Original Article

Evaluation of Serum Resistin, Visfatin, and Chemerin Levels in Patients with Lung Cancer and Chronic Obstructive Pulmonary Disease

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Abstract

OBJECTIVES: Cachexia is an important problem in lung cancer and chronic obstructive pulmonary disease (COPD). Some studies report an association between adipokines and cachexia. Our study aimed to investigate the association of three novel adipokines, resistin, visfatin, and chemerin, with lung cancer and COPD.

MATERIALS AND METHODS: 30 patients with non-smallcell lung cancer, 30 patients with COPD, and 30 healthy volunteers were included in the study. Statistically significant weight loss was found in COPD and lung cancer groups compared with that in the control group ($p<0.001$). Among the biomarkers, only resistin levels were significantly higher in patients with cachexia than in patients without weight loss in all groups ($p=0.006$). Resistin level was significantly higher in patients with COPD ($p=0.002$). Visfatin level was significantly higher in the control group ($p=0.001$). We found that a higher biomass exposure resulted in a significant increase and decrease in resistin ($p=0.007$) and visfatin levels ($p=0.001$), respectively, in the patient groups. For all groups, no statistically significant relationship was found between chemerin levels and weight loss or other variables.

RESULTS: No significant relationship was found between the biomarkers and lung cancer type, tumor stage, lymph node stage, and metastasis stage. There was no relationship between the biomarkers by tumor, node, and metastasis and COPD stages ($p>0.05$). We observed no findings strong enough to support the use of these molecules as markers of disease stage or cachexia.

CONCLUSION: Resistin, visfatin, and chemerin cannot be used as potential biomarkers for lung cancer or COPD or for disease stage or cachexia.

KEYWORDS: Adipokines, cachexia, chronic obstructive pulmonary disease, lung cancer

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INTRODUCTION

Respiratory tract diseases are the leading cause of death worldwide. Among these, lung cancer and chronic obstructive pulmonary disease (COPD) are the leadingdiseases with regard to mortality [1]. Lung cancer is usually already in an advanced stage at the time of diagnosis, and most patients have no chance of successful treatment. COPD is a chronic, progressive disease that severely affects the patients' quality of life. Weight loss is observed in certain disease stages in lung cancer and COPD, impairing quality of life and making the treatment more challenging. Cachexia is a clinical syndrome characterized by significant weight loss together with anemia and decrease in appetite [2]. In the literature, there are studies investigating the association between malignancies and adipokines [3, 4]. However, there are few studies investigating molecules other than leptin in COPD [5]. Although some studies report an association between adipokines and cachexia, some studies indicate otherwise.

Adipokines are protein biomolecules that are released from the adipose tissue. As recently described, adipose tissue is a highly active organ of the endocrine and immune systems. In vitro studies have demonstrated that some adipokines trigger the growth and proliferation of cancer cells. In addition, many clinical studies have reported that adipokines are significantly related to the tendency for tumor development, pathogenesis, and prognosis [6, 7]. Resistin, visfatin, and chemerin are newly described adipokines, and in our study, we investigated the role of these adipokines in lung cancer and COPD and their relationship with cachexia.

MATERIALS AND METHODS

This was a randomized controlled study conducted between July 2014 and March 2016 after obtaining ethics approval (approval no: 2014/85) from the Medical Faculty Ethics Committee. Thirty patients with newly diagnosed, untreated, and

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Table 1. Demographic data and biomarker levels of patients

	LC	COPD	Control	Overall	
	Mean±SD or median , minimum, maximum				p
Age, years	63, 41, 83[a]	65, 46, 81[a]	39, 28, 84[b]	60, 28, 84	**<0.001***
BMI, kg/m^2	24.71±3.89	25.61±6.16	27.55±4.16	25.96±4.93	0.073
Smoking, pack-years	50, 30, 100[a]	50, 10, 125[a]	13, 5, 27[b]	45, 5, 125	**<0.001***
Asbestos, years	30, 6, 50[a]	22, 9, 80	15, 5, 50[b]	25, 5, 80	**0.022***
Resistin, ng/mL	1.35±0.84	1.89±1.17[a]	1.09±0.56[b]	1.44±0.94	**0.002***
Visfatin, ng/mL	5.23±5.40	4.66±6.22[a]	8.03±6.64[b]	5.98±6.22	**0.009***
Chemerin, ng/mL	3.46±4.11	4.68±5.74	3.29±2.49	3.81±4.37	0.592

BMI: body mass index; LC: lung cancer; COPD: chronic obstructive pulmonary disease; p: statistical comparison between groups

histopathologically confirmed non-smallcell lung cancer (14 with adenocarcinoma adenocancer and 16 with squamous cell lung cancer) and 30 patients with mostly moderate-to-severe COPD, who were admitted to the chest diseases outpatient clinic, were included in the study. Thirty healthy volunteers without any diseases without other diseases were included in the study in the control group. Informed consent was obtained from all enrolled participants, and the demographic data of the participants were recorded. Patients with lung cancer were staged using tumor, node and metastasis (TNM) 7 [8] staging system. The results of pulmonary function tests and arterial blood gas analyses of patients with COPD were obtained from the hospital information system. Patients with COPD were categorized by the 2014 updated Global initiative for chronic Obstructive Lung Disease (GOLD) [9] classification. Patients with COPD underwent lung computed tomography scan to exclude any underlying pulmonary malignancy. For all participants, current body weight was compared with the body weight value measured 3 months ago. The subjects with a weight loss of more than 5% over the previous 3 months were considered to have cachexia. Asbestos and biomass exposure was questioned. Exposure was confirmed in subjects with asbestos or biomass exposure of 10 years or more. Blood samples were taken from all participants between 07:00 and 09:00 in the morning after overnight fasting. Lipid profiles and hemoglobin A1c levels were analyzed in the collected blood samples. In addition, blood samples of 5 mL were centrifuged at 5000 rpm for 5 minutes, and the obtained serum samples were transferred into 1.5-mL Eppendorf tubes and stored at -80°C until the analysis. Following collection, all samples were randomly numbered and submitted to the biochemistry laboratory for analysis. Samples were analyzed in the laboratory by enzyme-linked immunosorbent assay (ELISA) using Human Resistin Platinum ELISA kit (Bender MedSystems GmbH, Vienna, Austria), human visfatin ELISA kit (Sunred Biological Technology Co., Ltd., Shanghai, China), and human chemerin ELISA kit (Boster Biological Technology Co., Ltd., Pleasanton, CA, USA). The obtained data were recorded.

MAIN POINTS

- Resistin, visfatin, and chemerin cannot be used as potential biomarkers in patients with lung cancer or COPD.
- Resistin, visfatin, and chemerin cannot be used as a markers of disease stage or cachexia.
- Relationship between indoor air pollutants (e.g., biomass and asbestos) and adipokines.

Statistical Analysis

Statistical Package for the Social Sciences 19.0 software (IBM Corp.; Armonk, NY, USA) was used for the analysis of data. Parametric group comparison tests were used to analyze the variables conforming to normal distribution. Student's *t*-test was used for the two independent groups, and one-way analysis of variance was used for multiple groups. Tukey's honestly significant different pairwise comparison tests were used for significant results. The groups showing differences have been indicated with superscripts (Table 1 [a, b] and Table 2 [a, b]). Mann-Whitney Utest for two independent groups was used to compare the variables not conforming to normal distribution, and Kruskal-Wallis test was used for multiple group comparisons. Paired comparisons of Kruskal-Wallis test were performed in multiple groups with general significance. Chi-square test with Monte Carlo correction was used to determine the relationship between qualitatively measured variables. Spearman's Rho correlation analysis was used to assess the correlation between the proportional scale variables. Significant results were shown with graphics. In all analyses, a p value of <0.05 was considered statistically significant at a type I error level of 5%.

RESULTS

The subjects' median age was 60 (range: 28-84) years in all groups. The mean body weight was 73.88±16.08 kg. In all groups, 84.4% of the participants were male. The proportion of patients with a history of smoking was 76% (median: 50 pack-year) among the patients with lung cancer and COPD. The mean length of asbestos and biomass exposure was more than 20 years in the patients with lung cancer and COPD (Table 2). Approximately half of the patients with lung cancer had stage 4 disease (43.3%) and one-third had stage 3b disease (33.3%). The rest of the patients had stage 3a (13.3%), stage 2b (6.7%), and stage 2a (1.1%; n=1) disease. More than half of the patients in the COPD group had GOLD D disease (57.1%; n=20).

Table 2. Biomass and asbestos exposure

		LC n (%)	COPD n (%)	Control n (%)	p
Biomass exposure	Yes	22 (73.3)[a]	22 (73.3)[a]	8 (26.7)[b]	<0.001*
	No	8 (26.7)[a]	8 (26.7)[a]	22 (73.3)[b]	
Asbestos exposure	Yes	27 (90)[a]	26 (86.7)[a]	11 (36.7)[b]	<0.001*
	No	3 (10)[a]	4 (13.3)[a]	19 (63.3)[b]	

LC: lung cancer; COPD: chronic obstructive pulmonary disease; SD: standard deviation; BMI: body mass index, [a, b]: p values are significant for comparison of groups marked with "a" and "b"; * Statistically significant difference; p: statistical comparison between groups

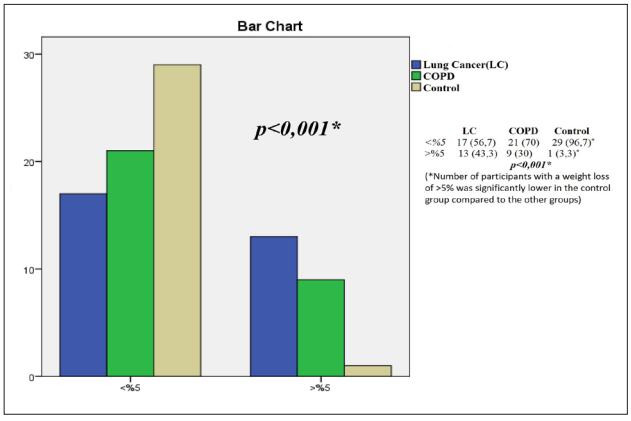

Figure 1. Participants with a weight loss of more than 5% over 3 months

Weight loss was higher in lung cancer and COPD groups than in the control group (p<0.001), and no significant difference was found between COPD and lung cancer groups in terms of weight loss (Figure 1). Sex had no significant effect on the measured markers.

The biomarkers resistin and chemerin were higher in patients with COPD, and visfatin was significantly higher in the control group (Figure 2).

Biomass exposure had a significant effect on resistin and visfatin levels. Resistin was higher and visfatin was lower in subjects with biomass exposure. Approximately one-third of patients had weight loss. Only resistin had a significant effect (p=0.002) on patients with weight loss.

No significant relationship was found between the biomarkers and lung cancer type (adenocarcinoma or squamous cell lung cancer), tumor stage, lymph node stage, and metastasis stage. There was no relationship between the biomarkers by TNM and GOLD stages (p>0.05) (Figure 3). There was no significant correlation between the resistin, visfatin, and chemerin levels in the lung cancer, COPD, and control groups. A positive and significant correlation was found only between age and chemerin levels (r=0.426; p=0.019). No significant correlation was found between the markers among patients with COPD. Resistin, visfatin, and chemerin levels were not different in patients with lung cancer with cachexia. It was observed that cachexia was effective on visfatin levels in patients with COPD (p=0.031). The mean

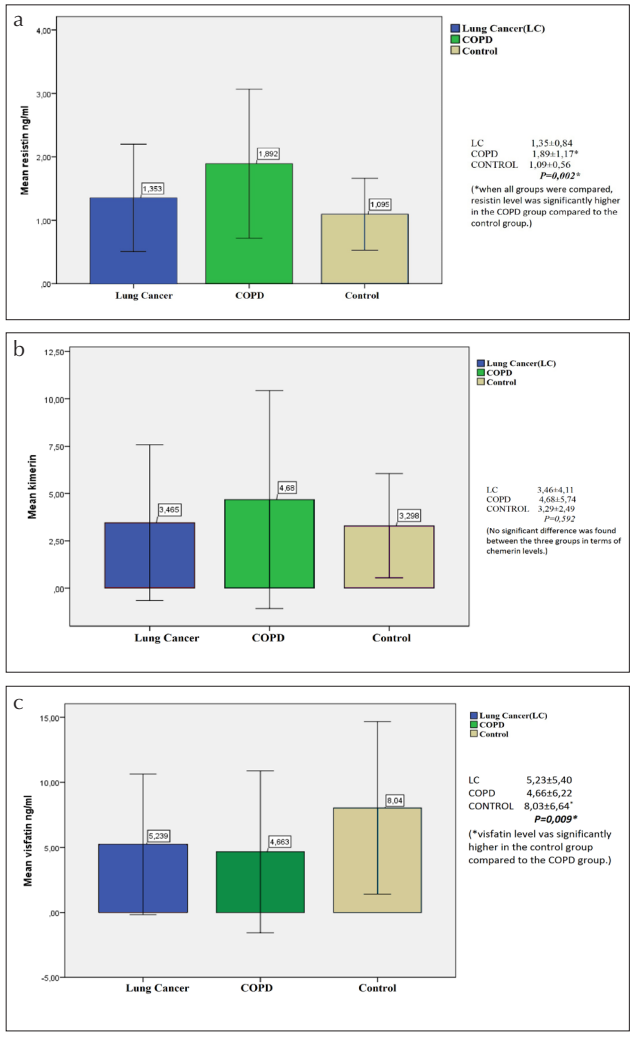

Figure 2. a-c. Comparison of biomarkers by groups

visfatin level was as high as 9.82±7.29 ng/mL in four patients with cachexia and as low as 3.87±5.80 ng/mL in patients without cachexia.

When the marker levels were compared by GOLD grades in patients with COPD and by TNM stages in patients with lung cancer, marker levels were not significantly different by GOLD grades or lung cancer stages. It was found that visfatin level increased with disease stage, and there was no increase or decrease in resistin and chemerin levels.

Among the biomarker levels, only resistin levels were significantly higher in patients with cachexia compared with that in patients without weight loss in all groups (p=0.006). Among the three groups, resistin level was significantly higher in patients with COPD (p=0.002). The visfatin level, however, was significantly higher in the control group (p=0.001) (Figure 2). We found that a higher biomass exposure resulted in a significant increase in the resistin level (p=0.007) and a significant decrease in the visfatin level (p=0.001) in the patient groups. Again, high asbestos exposure levels were associated with low visfatin levels (p=0.001). For all groups, no statistically significant relationship was found between chemerin levels and weight loss or other variables.

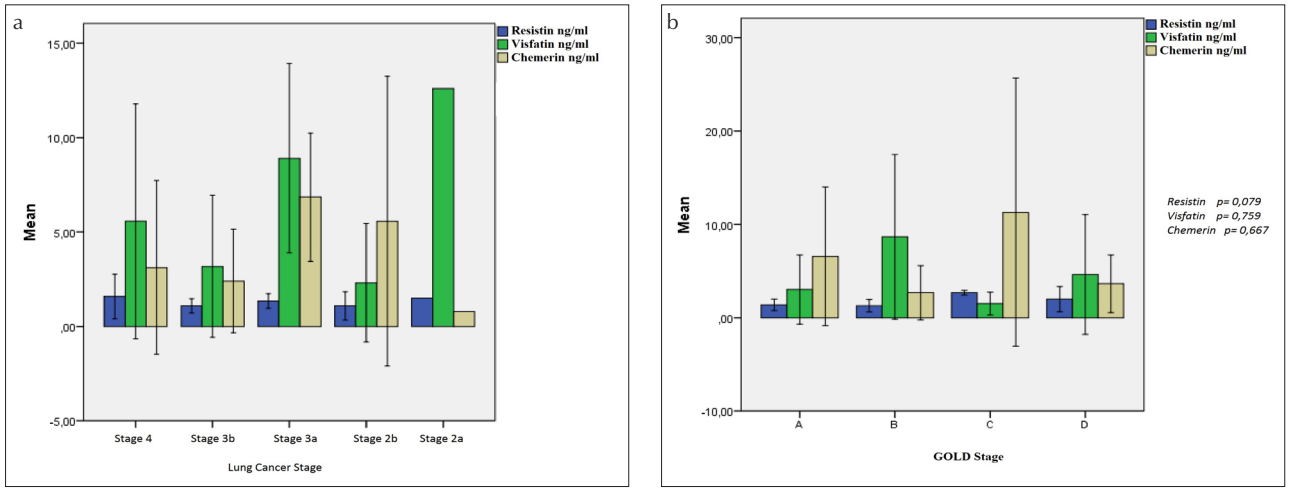

Figure 3. a, b. Marker levels by disease stages in patients with lung cancer patients and COPD. LC: lung cancer; COPD: chronic obstructive pulmonary disease; COLD: Global initiative for chronic Obstructive Lung Disease
(No statistically significant difference was observed in biomarker levels by lung cancer stages and GOLD stages)

DISCUSSION

Cachexia is a clinical syndrome characterized by significant weight loss together with disorders, such as a decrease in appetite and anemia, and it is mostly seen in patients with cancer although it can also be seen in other systemic diseases. Cachexia is an important problem in lung cancer and COPD. Cachexia has a significant effect on treatment success and quality of life of patients. Many hormones and mediators play roles in the pathogenesis of cachexia. A significant proportion of these are released from the adipose tissue. As recently described, adipose tissue is a highly active organ of the endocrine and immune systems. Leptin was first described in 1994 [10], and its association with many diseases was investigated in the following years. Today, it is known that the adipose tissue secretes more than 20 hormones and signal molecules that play roles in many biological events related to the autocrine and paracrine systems, vascular system through blood circulation, energy and glucose metabolism, reproduction, bone metabolism, and immunity [11]. Resistin, visfatin, and chemerin are newly described biomolecules and have not been investigated in many studies. Many clinical studies have reported that adipokines are significantly associated with the tendency for tumor development, pathogenesis, and prognosis [11, 12]. In a study investigating serum leptin levels in patients with lung cancer who have and do not have cachexia, serum leptin concentration was significantly lower in those with cachexiathan in those without cachexia and control patients [13].

In a review of critical patients and adipokine levels, resistin and visfatin levels were reported to increase irrespective of disease etiology in critical patients. This increase was reported to be related to organ failure and tissue inflammation [14]. In a study investigating the association between resistin, leptin, and lung cancer, resistin level was higher and leptin level was lower in thelung cancer group than those in the control group [15]. In addition, in our study, resistin level was higher in the lung cancer group than in the control group, but the difference was not statistically significant. Furthermore, visfatin level was higher in healthy volunteers than in the patients in our study, which was in contrast with the results from the available studies. In a study conducted in 2009, the relation between chemerin and lung cancer was investigated in 42 patients with lung cancer and 32 healthy volunteers; it was demonstrated that chemerin was not related to lymph node metastasis, stage, and pathological type, while chemerin levels were significantly higher in patients with lung cancer than in healthy volunteers, and the authors proposed that chemerin could be a diagnostic marker [16]. In a new study conducted by Xu et al. [17] in 2017, chemerin levels were significantly higher in patients with non-smallcelllung cancer than in healthy volunteers, and the higher chemerin level was reported to be related to the TNM stage, lymph node metastasis, and distant metastasis. In our study, however, chemerin level was higher in both patients with lung cancer and COPD than in healthy volunteers, but this increase was not statistically significant. Moreover, no relationship was noted between the increase in chemerin levels and TNM stage or tumor type.

Approximately 25% of patients with COPD develop cachexia, and this is associated with a severe decrease in patient survival. Only leptin was investigated in the studies assessing the association of adipokines with COPD and weight loss. Takabatake et al. [18] in their study found that serum leptin levels were low in patients with weight loss and increased with weight gain. This finding was not completely clear as it applied to all patients with COPD except for patientswith cachexia. In their study, Schols et al. [19] found that leptin levels were significantly lower in patients with emphysematous COPD than in patients with COPD with predominant chronic bronchitis. However, lean body mass was same in both groups, and it was observed that the decrease was in the adipose tissue mass. In addition, it has been reported that leptin stimulates inflammatory cytokines [20, 21]. In the light of all these studies, it was emphasized that leptin cannot be a marker for cachexia. KumorKisielewska et al. [22], in their study, found that leptin and resistin levels were higher in patients with COPD than in healthy subjects, and they reported that this could be related to the increased systemic inflammation in COPD. In addition, in our study we found that resistin level was high in patients with COPD and was related to weight loss.

The limitations of the study and the factors that may have affected the study results included the low number of patients in the groups, the fact that patients with advanced stage were included in the lung cancer and COPD groups, and the lower mean age in the control group than in the other two groups.

In conclusion, this study investigated the relationship between cachexia and the biomarkers released from the adipose tissue in lung cancer and COPD. It was concluded that resistin, visfatin, and chemerin cannot be used as potential biomarkers in patients with lung cancer and COPD. We observed no findings strong enough to support the use of these molecules as markers of disease stage or cachexia. However, higher levels of visfatin in the control group and in subjects with low biomass and asbestos exposure were considered as a result that differed from the literature.

Ethics Committee Approval: Ethics committee approval was received for this study from Necmettin Erbakan University Meram Medical Faculty. (2014/85)

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M. G., A. Z.; Design - A. Z., M. G.; Supervision - A. Z., C. K., S. D.; Resources - A. Z., M. G.; Materials - A. Z., C. K., S. D., M. G.; Data Collection and/or Processing - M. G., İ. K., A. Z.; Analysis and/or Interpretation - M. G., İ. K., A. Z., C. K.; Literature Search - M. G., S. D., A. Z.; Writing Manuscript - M. G., A. Z., İ. K.; Critical Review - A. Z., C. K., S. D., M. G.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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