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BMI and adipocytokine changes in COPD exacerbation and stable COPD

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COPD is described by progressive airflow restriction and recurrent acute exacerbations, which is caused by inflammatory response occurring in lungs as a result of chronic inhalation of harmful particles and gases. The study was designed to determine the link of interleukin-6 (IL-6), adiponectin and visfatin with BMI and oxidant/antioxidant balance in Chronic Obstructive Pulmonary Disease (COPD), a systemic disease. The study comprised control (n=20), patients with COPD (n=37) from the Chest Diseases Clinic of Firat University Hospital. The serum MDA, IL-6, Visfatin and Adiponectin levels were evaluated by ELISA. Also, Pulmonary Function Tests were done. There was no significant difference between control and patients with COPD in terms of sex and age averages. On the contrary, BMI levels were statistically significantly lower in COPD group compared to the controls. MDA and adiponectin levels were higher, IL-6 and visfatin levels were lower in COPD groups contrary to controls. It was thought that the level changes of these parameters (MDA, IL-6, visfatin and adiponectin) may be an important factor in the development of COPD and in monitoring the treatment of COPD-related diseases.

Keywords: Adiponectin, Chronic obstructive pulmonary disease (COPD), Interleukin-6, Malondialdehyde (MDA), Visfatin

Chronic obstructive pulmonary disease (COPD) is a disease characterized by progressive airflow limitation and recurrent acute exacerbations, which is caused by inflammatory response occurring in lungs as a result of chronic inhalation of harmful particles and gases[1]. COPD affects small and large airways in lung, lung parenchyma and pulmonary vascular bed, and also other systems[2].

Causes of body composition change (fat-free mass, fat mass and bone mineral content, *etc*.) accepted as an important cause of comorbidity in COPD[3], the increase in energy consumption that is associated with respiration developing in parallel to the increase in respiratory act, negative energy balance caused by the impairment in metabolic and functional capacities are used to explain this change[4]. In the pathogenesis of COPD, in addition to genetic factors, environmental factors, inflammation and especially oxidative stress play an important role[5]. Activated inflammatory cells, neutrophils and alveolar macrophages lead to endogenous oxidant production in patients. Increased oxidative burden damages all the cellular macromolecules (lipid, protein and DNA)[6].

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Adiponectin, the richest adipokine in human plasma, has been reported to have both pro-inflammatory and anti-inflammatory effects[7,8]. Therefore, while serum level of adiponectin is high in some human studies[9,10], it is low in others[11,12]. Visfatin is a proinflammatory cytokine which is secreted from visceral fat tissue rather than subcutaneous fat tissue, exhibits an insulin-like effect by binding to insulin receptors and has immunomodulatory effects in inflammation, natural immunity regulation[13]. It was reported that evaluated the relationship of nesfatin and visfatin with inflammation activity, severity of symptoms, and lung function in men with emphysema and COPD[14]. IL-6, one of the inflammatory cytokines, increases in different lung diseases and is a by-product of ongoing inflammation in the lung[15]. In a study conducted by Liang *et al*., leptin and IL-6 levels in the serum and sputum were higher in patients with acute exacerbation of COPD compared with stable COPD and control patients. Therefore, they were suggested that leptin and IL-6 levels were associated with the severity of COPD[16].

It was aimed to detect the association of interleukin-6 (IL-6), adiponectin and visfatin with BMI and oxidant/antioxidant balance in COPD, a systemic inflammatory disease.

Materials and Methods

Patient selection

37 patients who were followed with a diagnosis of COPD acute attack in the Chest Diseases Clinic of Firat University Hospital were included in the study. The diagnosis of COPD acute attack was defined as a situation which is characterized by an increase in respiratory disorder and a decrease in the daily performance, change in sputum amount and color, exacerbation in coughing, high fever and/or deterioration in mental status in a case progressing stabile, and which may require change in an ordinary drug treatment with acute onset. Age, gender, duration of disease and smoking histories of the cases were questioned, and their body mass indexes were calculated by measuring weight and height.

The presence of systemic, allergic, neoplastic or immunologic diseases, the determination of reversibility in pulmonary functions and the presence of coexisting lung disease to COPD were considered as the exclusion criteria from the study. Control group was formed by randomly selecting 20 cases who were in the same age group and gender with COPD patients, who has normal spirometric lung functions and who had no history of lung and systemic infection and regular use of drug in the last month. They were also nonsmokers.

Blood was taken from COPD patients for 2 times which were in the acute period (1st day and on the 15th day after treatment, and 5 mL of blood was taken from the healthy control group for 1 times, and serum levels were studied in Medical Biochemistry Laboratory. From COPD patients and the healthy control group, venous blood samples were taken into gelled chemistry tubes between at 08:30-09:30 after 10 h of fasting, and their serums were separated by centrifuging for 5 min. at 4000 rpm. Serum samples were separated into portions and stored at −80°C until the day of analysis. Samples were studied by warming to room temperature (23–25.5°C) after taken out of the deep freezer.

Detection of Malondialdehyde (MDA)

As an indicator of lipid peroxidation, MDA levels were measured using appropriate MDA kit (Immuchrom GmbH Company, Hessen, German) by High-performance liquid chromatography (HPLC). MDA, which is converted into fluorescence products with a derivatising agent, added reaction solution. The absorbance of MDA was measured at 515 nm (excitation), at 553 nm (emission) by spectrophotometric detector. The results were given as nmol/mL.

Determination of serum levels of IL-6, Visfatin and Adiponectin

Serum concentration of IL-6 (Boster Biological Technology, Ltd., Pleasanton, CA, EK0410) Visfatin (Adipo Bioscience, Santa Clara, CA, USA, SK00121-01) and adiponectin (Boster Biological Technology, Ltd., Pleasanton, CA, EK0595) levels were measured by a commercially available sandwich enzyme-linked immunosorbent assay according to the manufacturer's protocol. Absorbance of standards and samples was read at 450 nm. Automatic ELx50 Biotek plate washer and ELx800 plate reader was used in ELISA studies. Manufacturer average intra-assay and inter-assay coefficients of variation were <10% for IL-6, visfatin and adiponectin.

Measurement of Pulmonary Function Tests

Pulmonary function tests were performed at least three measurements using nose plugs, in a sitting position, at room temperature in Firat University Chest Diseases Clinic and the best results were evaluated. FEV1, FVC and FEV1/FVC ratio were measured and recorded. The data was interpreted according to the European Respiratory Society estimates.

Statistical Analyses

All results were presented as means ± SD and analyzed using one-way analysis of variance (ANOVA). The LSD test was used for comparisons between groups. $P \leq 0.05$ was considered statistically significant. Statistical analysis was performed using the SPSS 22.0 statistical software package (SPSS Inc., Chicago, IL, USA) for this purpose. Bivariate correlation analysis (calculation of the Pearson coefficient) was used to assess the correlation of serum visfatin and adiponectin levels to each parameter.

Results

There was no any statistical difference between the patients and the control group in terms of sex and age averages. BMI values were statistically significantly lower in COPD group compared to the controls ($P < 0.001$). Demographic features of the study group are shown in (Table 1).

Mean FEV1, FVC and FEV1/FVC values of COPD patient group (1st, 15th day and total) were quite lower

Table 1 — Demographic Characteristics of the Study Group

	Control Group (n=20)	COPD Group (n=37)
Age (year)	60.05± 5.71	61.59± 5.91
Sex (M/F)	20/0	37/0
BMI (kg/m^2)	23.67±1.98	21.16±2.84*

*P <0.001 compared with control group

Table 2 — Pulmonary Function Test Parameters of the control and patient group with COPD (1, 15 days and total), and serum MDA, IL-6, visfatin and adiponectin levels

	Control Group	COPD Group (1st Day)	COPD Group (15th Day)	COPD Group (Total)
BMI	23.67±1.98	21.16±2.84*	21.63±2.89**	21.38±2.86*
FEV1 (%pred)	87.95±4.55	31.05±11.08*	39.19±13.59*	34.76±12.86*
FVC (%pred)	87.40±4.67	47.32±12.87*	55.55±17.52*	51.07±15.61*
FEV1/FVC	88.45±5.67	49.27±10.19*	50.13±11.46*	49.66±10.71*
MDA (nmol/mL)	0.64±0.22	1.61±0.24*	1.36±0.23*	1.50±0.27*
IL-6 (pg/mL)	1.23±0.42	1.11±0.08**	1.10±0.04**	1.11±0.06**
Visfatin (ng/mL)	9.71±1.36	8.37±1.26*	8.64±1.32**	8.49±1.29*
Adiponectin (ng/mL)	22.51±10.69	151.74±93.68*	162.89±104.79*	156.83±98.30*

*P< 0.001 compared with control group, **P< 0.05 compared with control

compared to the control group (P< 0.001 for three parameters). Serum visfatin and IL-6 levels were statistically significant lower in COPD group compared to the controls. MDA and adiponectin levels were statistically significant higher in patient groups compared with controls (Table 2).

There was a positive correlation between serum IL-6 levels and visfatin levels (r: 0.330, p=0.046), and a negative correlation between adiponectin (r= −0.375, P =0.022) patient groups (Table 3).

Table 3 — Correlation between adipokines and other parameters in patients with COPD exacerbations (n=37)

	Visfatin (ng/mL)	Adiponectin(ng/mL)
IL-6 (pg/mL)	*Rho*= 0.330	*r*= −0.375
	P= 0.046	*P*= 0.022
BMI	*Rho*= −0.228	*r*= −0.225
	P= 0.175	*P*= 0.180
FEV1 (% pred)	*Rho*= −0.316	*r*= −0.144
	P= 0.057	*P*= 0.395
FVC (% pred)	*Rho*= 0.025	*r*= −0.279
	P= 0.885	*P*= 0.094
FEV1/FVC	*Rho*=−0.308	*r*= 0.024
	P= 0.064	*P*= 0.886

Discussion

Decreases in bone mass in the patients with low BMI and increase in fatty tissue in obese patients were associated with the impairment in health status and increased mortality[17]. It was also indicated that low BMI is a risk factor for COPD development[18]. The reducing BMI as a result of dyspnea in COPD, inadequate food intake due to the difficulty in food digestion and excessive apoptosis in skeletal muscles based on systemic inflammation has been defined as an independent marker of mortality and morbidity secondary to the disease[19]. The fact that BMI values were statistically significantly lower in COPD patient group, in which all the patients are male, compared to the control group in our study supports the study results above. The relationship that we detected between BMI values and respiratory functions of the patients with COPD exacerbation gives rise to the thought that BMI assessment is important in disease pathogenesis. Moreover, understanding the weight loss mechanisms in COPD and minimizing the weight loss have been found important in terms of survival duration and fighting against the disease[20].

Oxidative stress and inflammation that are characteristic for COPD have synergistic effects on muscle breakdown[21]. As a result of excessive oxidant production of oxidant/antioxidant balance and/or breakdown of antioxidants in favor of the reduction thereof occurs oxidative stress[22,23]. Oxidative stress not only damages lungs but activates molecular mechanisms performing lung inflammation, as well[24]. Increased oxidative stress parameters and decreased BMI values in our study are parallel to these studies. MDA levels of COPD patient groups [1st, 15th day and total) were significantly higher than the controls in our study. This increase was even more apparent in patients with COPD exacerbation. This shows that oxidant effect increasing in COPD leads to lipid peroxidation. Similarly, MDA levels were statistically significantly high in COPD patients[25,26]. Likewise, in a lot of literature studies, MDA levels were higher in acute exacerbation period compared to the stable period in COPD patients similar to the data of our study. Again in these studies, the decreases detected in antioxidant enzyme levels indicate that oxidant/antioxidant balance is break down in favor of oxidants in COPD patients[27,28].

It is detected that in studies that are made considering the fact that pathology is not only limited to airways in COPD, but there are also the systemic effects, weight loss is associated with inflammatory cytokines such as serum IL-6 and TNF-α and adipocytokines such as serum leptin, adiponectin and

visfatin[29,30]. It is reported that adiponectin, which is among the adipokines regulating the energy metabolism and appetite, increases insulin sensitivity and the levels decrease in obese individuals as inflammatory response[31]. Anti-inflammatory effect of adiponectin manifests itself as the increase in plasma adiponectin levels in COPD individuals[32]. Carolan *et al*. also detected that increased plasma adiponectin levels in COPD are associated with lung emphysema and low bronchial capacity related to BMI decreasing at later ages leads to disease progression[32]. In our study, similarly, serum adiponectin levels were significantly higher both in COPD exacerbation and stable COPD groups compared to the controls. Significant increase of adiponectin levels in COPD groups with low BMI is parallel to the mechanisms stated above. These results give rise to the thought that hyperinflation and low BMI in COPD patients increase serum adiponectin levels with anti-inflammatory effect and contribute to the defense.

Intra-abdominal adipose tissue, an active endocrine organ, has a positive correlation with pro-inflammatory adipocytokines (IL-6, TNF-α and leptin) regulating insulin sensitivity and negative correlation with adiponectin[33]. When (1st, 15th day and total) serum IL-6 levels of COPD patient group were compared with the control group, there was a statistically significant decrease, and there was a negative correlation between decreased IL-6 levels and serum adiponectin levels ($r = -0.375$, $P = 0.22$). Except for the increase in acute phase proteins, functional effects of IL-6 in circulation has not been determined yet, but there is evidence regarding that it may be associated with skeletal muscle weakness[34]. It is shown that there is a correlation between the increased IL-6 concentrations in circulation and systemic inflammation degree in some comorbid diseases. Inflammatory mediators such as TNF-α, IL-lβ and IL-6 can be accepted as general markers of inflammation. However, IL-6 is not a simple inflammatory marker and has an active role in the pathogenesis of some diseases such as rheumatoid arthritis[35]. Studies claiming that IL-6 has a potential role in the pathogenesis in COPD and induced mucus IL-6 levels are inversely proportional to FEV1[36].

In addition to the studies stating that visfatin levels in circulation system of the patients losing excessive weight after the stomach surgery[37]. Both high[38] and low[39] visfatin levels were reported in COPD patient groups when compared to the control group. In our study, serum visfatin levels of COPD patient group (1st, 15th day and total) were statistically significantly lower when compared to the control group. Visfatin, along with TNF-α and IL-6, plays a key role in the regulation of inflammatory process[40]. COPD patient data studying on visfatin level are quite contradictory. In addition to the studies reporting high visfatin levels in COPD patients with low BMI[40,41], there are also studies detecting decreased visfatin levels[14,42]. In a study, it was reported that there is a positive correlation between low plasma visfatin levels and visfatin and IL-6 in COPD patients[14]. Similarly, in our study, there was a positive correlation between visfatin and IL-6 levels in COPD exacerbation patient group ($r = 0.330$, $P = 0.046$).

Conclusion

It was suggested that the level changes of MDA, IL-6, visfatin and adiponectin may be an important factor in the development of COPD. Meanwhile, the studies in which the correlation between systemic inflammation and weight loss during COPD is evaluated, although a lot of inflammatory markers are correlated with weight loss and other systems, the mechanisms could not be identified clearly. Methods should be developed by considering the effects of decreased BMI on the disease severity in the fight against COPD. Moreover, while treatment protocols for the increased inflammation and oxidative stress are developed, thanks to the assessments to be made in cytokine and protein changes with pro-inflammatory/ anti-inflammatory effect by considering the other systems accompanying the disease in addition to the respiratory system, early diagnosis and the treatment of the accompanying diseases, COPD morbidity and mortality can be reduced.

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Conflict of interest

All authors declare no conflict of interest.

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