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Original Research Article

Assessment of Serum Levels in Adipokines in Chronic Obstructive Pulmonary Disease (COPD)

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Abstract

Chronic obstructive pulmonary disease (COPD) is described as a non-reversible airway obstruction and having systemic inflammatory progress. Secreted proteins by adipose tissue called as adipokines, Apelin, Ghrelin, Nesfatin, Visfatin and Leptin, have role in energy metabolism and inflammatory responses in chronic inflammatory diseases. We sought to search the role of adipokines in COPD and better understand the pathogenesis of this disease. This study was performed with 35 COPD and 25 healthy Turkish individuals. The statistical power for the groups was calculated by two-tailed test, an 80% confidence interval, and an alpha level of 5% significance. Peripheral blood samples were collected and separated for serum. Serum levels of interested parameters were measured by ELISA. Results were presented as mean ± standard error of the mean (SEM). Statistical significances were analyzed by Mann-Whitney U test. We could observe statistically significant high serum levels of apelin and ghrelin in COPD. There was not significant change for serum levels of nesfatin, visfatin and leptin. Apelin and ghrelin may be considered as potentially new targets for diagnosis and treatment of COPD. We suppose that to understand COPD pathophysiology and cure it more efficiently it is necessary to clarify adipokines role in this disease.

Keywords: Adipokines, Apelin, Chronic obstructive pulmonary disease (COPD), Ghrelin, Leptin, Nesfatin, Visfatin

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined as a systemic and irreversible disease that results in airway obstruction (GOLD Guideline, 2014) and is attributed wit production of various adokines such as Apelin, Ghrelin, Nesfatin, Visfatin and Leptin. COPD is an inflammatory response of the lung parenchyma to harmful inhaled substances (Nakawah et al., 2013). COPD is the third leading cause of death worldwide after ischemic heart disease and stroke (Blf, 2019). In addition to the inflammatory process that develops in the lungs, there is low-grade systemic inflammation associated with the pathogenesis of comorbidities present in COPD (Agustí, 2007; Barnes et al., 2009; Wouters et al., 2009). In addition, it is unknown whether systemic inflammation is an extension of inflammation present in the lungs or whether pulmonary manifestations are a form of expression of this systemic disease (Barnes et al., 2009; Sinden et al., 2009). It has been suggested that advanced inflammation of the lung, hypoxia, and skeletal muscle dysfunction caused by inhaled toxic agents or disease pathogenesis cause the systemic inflammation observed in COPD (Agustí, 2007). Patients with COPD

have general malnutrition, low body mass index, and progressive skeletal muscle dysfunction, independent of permanent airway restriction (Wouters et al., 2009; Vestbo et al., 2013; Keogh et al., 2021). These abnormalities are independent of the degree of airway obstruction and contribute to the poor prognosis of the disease and mortality (Balasubramanian et al., 2006). Although the relationship between the adipose tissue-mediated inflammatory response and the systemic inflammation observed in COPD has been studied, the mechanisms of skeletal muscle dysfunction and malnutrition observed in the disease have not been fully explained yet (Wagner, 2008; Wouters et al., 2009).

Adipokines, also known as adipocytokines, are secreted by adipose tissue. In addition to regulating the energy metabolism of adipokines, they also play a role in the regulation of the inflammatory response in chronic inflammatory diseases (Fantuzzi, 2005; Ouchi et al., 2011). In this context, adipose tissue is accepted as an endocrine organ that synthesizes adipokines(Trayhurn et al., 2004; Cancello et al., 2004). As a result of the direct effect of changes in nutritional status, adipose tissue functions may change (Baranowska-Bik et al., 2017). The roles of adipokines in the inflammation process have increased the interest in adipokines in inflammatory lung diseases (Ali Assad et al., 2012; Chwalba et al., 2019; Zhang et al., 2018; Malli et al., 2010; Leivo-Korpela et al., 2014; Wang et al., 2022).

In the present study, we have tried to present a part of adipokines profile evaluation in COPD by studying the serum levels of apelin, ghrelin, nesfatin, leptin and visfatin. Thus, we hope we would have more clues about adipokines role in COPD and these can help us to understand the pathophysiology of this disease.

MATERIALS AND METHODS

Study Population

This study was performed with a total of 60 subjects (COPD patients) who were treated at Kütahya Health Sciences University, Faculty of Medicine, Department of Chest Diseases, Kütahya, Turkey.

Target Population Study Design

The Global Initiative for Chronic Obstructive Lung Disease's recommended criteria taken as the basis for the diagnosis of COPD (GOLD Guideline, 2014). Each subject received a personalized explanation of each operation before providing their written informed permission. The study protocol conforms to the ethical guidelines of Declaration of Helsinki and was approved by the Ethics Committee of Afyon Kocatepe University.

Sample Size Calculation

The statistical power for the COPD and control groups was calculated using a two-tailed test, an 80% confidence interval, and an alpha level of 5% significance. Thirty-five (19 males 16 females) unrelated patients with COPD were included as the patient group and 25 (14 males, 11 females) healthy age-matched subjects were included as the control group. All individuals were selected from the Turkish population.

Equipment and Reagents

Sampling techniques

Peripheral blood samples (5 mL) collected in tubes without EDTA from all subjects. They have been left at room temperature for approximately 15–20 min. to allow the blood to clot. Collected blood samples from each participant have been centrifuged the blood at 3000 rpm for 15 minutes to separate the fibrinogen precipitate and yieldserum. After centrifugation, all serum samples were stored at –80 ºC until Enzyme-Linked Immunosorbent Assay (ELISA) analysis.

Enzyme-Linked Immunosorbent Assay (ELISA) Analyses

The serum levels of apelin, ghrelin, nesfatin, visfatin and leptin were analyzed by ELISA kits without stimulation at Rel Assay Diagnostics Research Laboratories in Turkey. Chemiluminescence data were analyzed by an ELISA microplate reader (das, Digital and Analog Systems, Vimercate, MI, Italy).

Data Analysis and Presentation

Data were analyzed statistically. The SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) 16.0 package application was used to conduct the statistical analyses. The serum levels of relevant parameters were given as mean ± standard error of the mean (SEM). Statistical significances for each interested parameter between the two groups were analyzed by Mann-Whitney U test. Differences were considered significant at $p<0.05$.

RESULTS

The average age for COPD group was 53 (range: 42–63); for the control group was 49 (range: 40–58). Thirty-five unrelated patients with COPD (19 males, 16 females) were included as the patient group and 25 healthy age-matched subjects (14 males, 11 females) were included

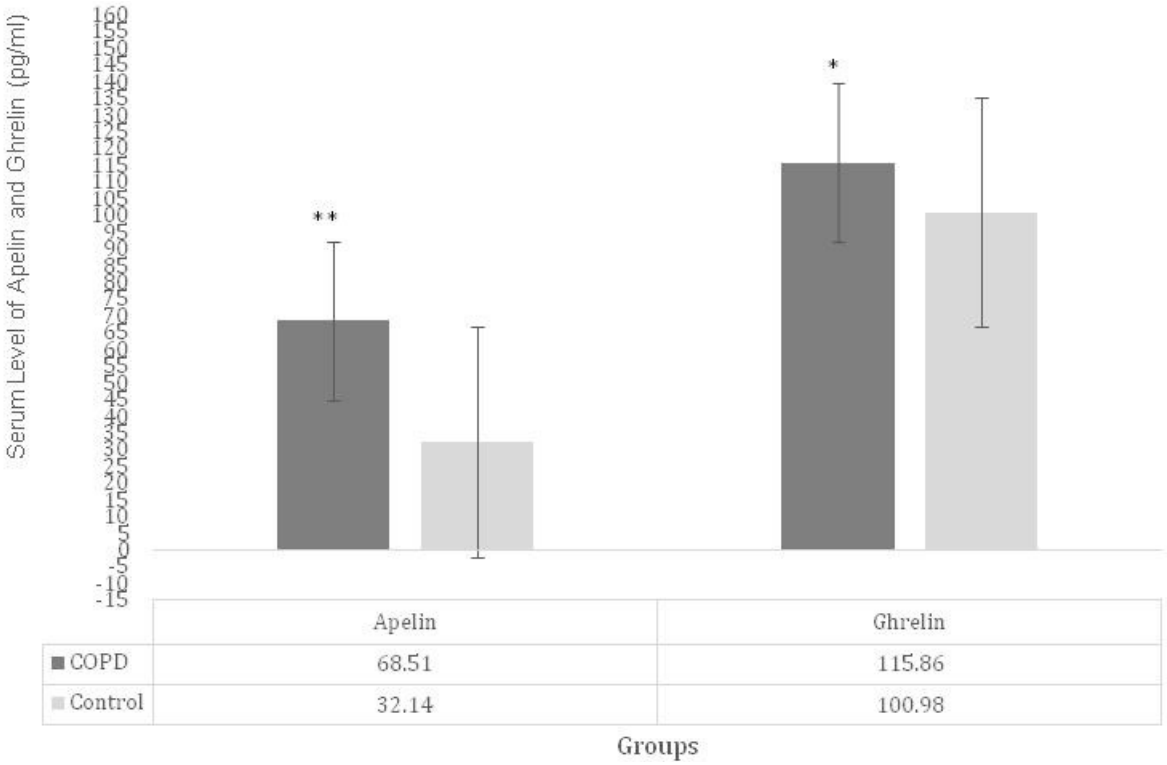

Figure 1. Serum Level of Apelin and Ghrelin in COPD and control groups
COPD; Chronic obstructive pulmonary disease.
*; $p < 0.05$ vs. control group.
**; $p < 0.01$ vs. control group.

Table 1. The comparisons of serum levels of nesfatin, visfatin and leptin between the patient and control groups.

	COPD	Control	P value
Nesfatin (pg/ml)	32.84 ± 1.11	24.18 ± 1.69	0.05
Visfatin (pg/ml)	0.1 ± 0.01	0.05 ± 0.01	0.062
Leptin (pg/ml)	105.20 ± 14.39	136.30 ± 14.19	0.053

Data are mean ± SEM.COPD; Chronic obstructive pulmonary disease.

as the control group. Age and gender mean differences between the two groups were not statistically significant ($p > 0.05$).

The mean of serum level of apelin was high, detected as 68.51 ± 5.8pg/ml in the COPD and 32.14 ± 3.7pg/ml in the control group. The mean of serum level of ghrelin was found as 115.86 ± 1.70pg/ml in the COPD and 100.98 ± 4.73pg/ml in the control group. We have observed that the serum levels of apelin and ghrelin were significantly higher in COPD group compared to the control group (respectively; $p = 0.003$, $p = 0.018$)(Figure 1).

The mean of serum level of nesfatin was high, detected as 32.84 ± 1.11 pg/ml in the COPD and 24.18 ± 1.69 pg/ml in the control group. The mean of serum level of visfatin was found as 0.1 ± 0.01 pg/ml in the COPD and0.05 ± 0.01 pg/ml in the control group. The mean of serum level of leptin was high, detected as 105.20 ± 14.39 pg/ml in the COPD and 136.30 ± 14.19pg/ml in the control group. Serum levels of nesfatin, visfatin and leptin were not significantly changed in the COPD group compared to control group (respectively; $p = 0.05$, $p = 0.062$, $p = 0.053$)(Table 1).

LITERATURE REVIEW

COPD, which is defined as permanent and irreversible airway narrowing and is a fatal but manageable disease worldwide, is often associated with systemic inflammation, skeletal muscle dysfunction, and diet-related body fat reduction. The severity of the airflow limitation is unrelated to these anomalies, which even

worsen mortality and prognosis (Zhang et al., 2018). Although we could not evaluate nutritional situation and body fat composition in our study, in the literature it was studied that changes in nutritional status due to various diseases and the resulting change in body fat content can change the hormonal activity of adipose tissue. There are few studies on the relationship between respiratory tract diseases and adipokines secreted from adipose tissue (Chwalba et al., 2019; Baranowska-Bik et al., 2017). In addition to malnutrition, a chronic systemic inflammatory process is usually observed in patients with COPD. In the literature, a significant decrease in body mass index and tissue digestion has been reported in COPD patients compared to healthy individuals (Chwalba et al., 2019; Liu et al., 2009). Although the roles of adipocytokines in various diseases have been studied, studies related to COPD and inflammation observed in the disease are insufficient (Chwalba et al., 2019). Another shortcoming that we should mention in our study is that it is not possible to look at inflammation parameters with known efficacy except for adipokines. Therefore, it is not possible to fully explain the connection of the adipokines we examined with known inflammation parameters in COPD.

Although the role of apelin, a peptide hormone secreted from fat and endothelial cells, in inflammation has been tried to be explained, its exact role in inflammation is not known (Tatemotoet et al., 1998; O'Dowdet et al., 1993; Yadavaet et al., 2021; Yoshiyaet et al., 2015; El-Shehabyet et al., 2010). It is known that proinflammatory factors can affect the expression of apelin, and vice versa, apelin can also affect proinflammatory factors (Daviaud et al., 2006). In addition, it has been suggested that apelin may play an important role in the development of lung diseases (Fan et al., 2015; Visser et al., 2010). It is stated that apelin should be evaluated as a target therapeutic agent in inflammation and diseases in the body, to consider the performance of apelin in inflammation (Wang et al., 2022). According to our observation there is no study describing the serum level of apelin in COPD patient. Our results indicate that serum levels of apelin in COPD is significantly higher compared to control group. If we can consider that individuals in the COPD group were newly diagnostic and had not medicated, we may conclude that apelin can be an indicator for COPD. Additionally, we can conclude that apelin is not just serum marker for COPD and can be a trigger for inflammation answer against to COPD as homeostatic agent.

In this study it was observed that serum Ghrelin levels in the COPD group were significantly increased compared to the control group as reported in the literature. Ghrelin, a peptide hormone of 28 amino acids that was initially identified in 1999, has a variety of roles in the body, including regulating digestion, energy and glucose metabolism, and nutrition (Kojima et al., 1999; Müller et al., 2015; Colldén et al., 2017). Although ghrelin is not secreted from the adipose tissue, it is known that it influences the adipose tissue and, in addition, the circulating ghrelin level increases due to weight loss (Sumithran et al., 2011; Tsubone et al., 2005). It has anti-inflammatory properties and controls the release of cytokines that promote inflammation (Erşahın et al., 2011). Additionally, it has been discovered that lung disorders including COPD, asthma and pulmonary hypertension change ghrelin levels. Recently, several studies looked at the amount of ghrelin in the plasma and serum of COPD patients and hypothesized that it might act as a biomarker for weight loss and pulmonary dysfunction in COPD. Although some these studies found that COPD patients had greater levels of circulating ghrelin, the others revealed the opposite findings (Toru et al., 2015; Colldén et al., 2017; Itoh et al., 2004; Wang et al., 2014; Ying et al., 2008; Piehl-Aulin et al., 2009; Luo et al., 2005). In support of some of the literature information we have mentioned, increased Ghrelin level in the COPD compared to control may be related to the decreased body fat ratio and may be one of the markers of COPD disease. We now want to call attention to ghrelin's ability to reduce inflammation, which may play a significant role in asthma. We speculate that this rise in ghrelin may be related to its ability to block the production of pro-inflammatory cytokines.

Nesfatin-1 is a peptide secreted from adipose tissue and controls appetite and body weight (Oh-I et al., 2006). Subsequent studies have shown that nesfatin regulates inflammatory responses and cell apoptosis in rats and has protective effects on the heart in humans (Tang et al., 2012; Angelone et al., 2013). There are studies in the literature on changes in fat mass in lung cancer (Cetinkaya et al, 2013) and on cystic fibrosis and nesfatin(Cohen et al., 2013).

Visfatin is produced mainly by granulocytes and monocytes, but also by macrophages and adipocytes (Friebe et al., 2011; Curat et al., 2006). Visfatin is a proinflammatory cytokine responsible for the regulation of inflammation and natural immunity (Moschen et al., 2007; Luk et al., 2008). In the lungs, visfatin is associated with acute lung injury, and inhibition of visfatin synthesis has been shown to reduce inflammation and apoptosis in viral infections in the lungs (Ye et al., 2005; Gao et al., 2011). A study has indicated that nesfatin and visfatin have a positive correlation with systemic inflammation in COPD and play a role in inflammatory processes. In the same study, he explained the relationship of visfatin with decreased pulmonary diffusion capacity. The results of this study indicate that nesfatin and visfatin may have a proinflammatory role in the pathogenesis of the emphysema type of COPD (Leivo-Korpela et al., 2014).

In another study, it was found that plasma visfatin levels in the COPD group increased significantly compared to the healthy group. This increase has been associated with increased local and systemic inflammation in COPD patients, which may increase

visfatin expression, and it has been argued that an increase in visfatin levels may promote inflammatory processes in COPD. In this context, the study claims that visfatin is both a novel marker of inflammation and possibly an important proinflammatory adipocytokine in COPD (Liu et al., 2009). Another study shows that the increased visfatin level in people with COPD is due to hypoxia (Moschen et al., 2007).

In our study, serum nesfatin and visfatin levels were increased in the COPD group compared to the control group, although not significantly. It is not possible to fully explain the causality of this increase, which is compatible with the literature. There are reasons for this, such as the relatively small number of our study groups, the fact that our patient group consisted of individuals who were first diagnosed and did not start drug treatment, and that no other classification was made. However, we think that nesfatin and visfatin may have a proinflammatory role in the pathogenesis of COPD. Additionally, we further studies are needed to assess whether adipokines can be used as biomarkers or anti-inflammatory drug targets for phenotyping or subgrouping patients with COPD. In addition, we can say that further studies are needed to evaluate whether nesfatin and visfatin can be used as biomarkers or anti-inflammatory drug targets for the phenotyping of patients with COPD.

Leptin is a 167 amino acid adipokine mainly synthesized and secreted from white adipose tissue (Zhang et al., 1994; Friedman et al., 1998). Some studies have shown leptin production in human lung tissue (Vernooy et al., 2009; Bruno et al., 2009). It has been reported that leptin secretion is induced by insulin and glucocorticoids (Widjaja et al., 1998). Its main function is to regulate nutrition (Saladin et al., 1995). In addition to regulating metabolic functions, leptin has a role in both innate and acquired immunity (Matarese et al., 2005; Tilg et al., 2006). In inflammation, an increase in leptin levels in the acute state and a decrease in the chronic state have been observed (Popa et al., 2005). Studies have focused on the disturbances in energy balance, which are responsible for weight and muscle loss in COPD, due to irregularities in leptin synthesis and secretion. However, no significant increase in leptin levels was demonstrated in cachectic COPD patients (Andreas et al., 2005; Takabatake et al., 1999).Although no significant change was observed in leptin levels in individuals with COPD compared to healthy individuals, there are studies showing that sexual disorders, glucose tolerance disorders, pulmoner infection frequency and osteoporosis observed in COPD are caused by low leptin levels (Takabatake et al., 1999; Vondracek et al., 2009). In COPD patients with cachectic and frequent attacks, higher leptin levels were found compared to COPD patients with normal weight (Calikoglu et al., 2004). Studies argue that leptin plays a role in the regulation of the local inflammation response observed in the airways in COPD patients (Bruno et al., 2005).

In our study, we found a statistically insignificant decrease in serum leptin levels in the COPD group compared to the control group. In the light of the information in the literature we have mentioned, this decrease may be an indicator of chronic inflammation of the individuals in our patient group. Considering that leptin levels do not vary depending on body mass index in COPD patients, we think that leptin should not be considered as a biomarker for the diagnosis of COPD, but as an anti-inflammatory agent whose increase is supported for the regulation of inflammation observed in COPD.

CONCLUSION

In our study, we investigated the serum levels of some adipokines and ghrelin in the control group and the newly diagnosed COPD group who did not receive any medication and presented their comparison between the two groups. All individuals included in our study are from the Turkish population. In this context, we think that the relevant parameters may differ between populations in terms of genetics. We can conclude that further studies are needed to evaluate whether the parameters in our study can be used as targets in the diagnosis and treatment of COPD in line with the results we have presented, the literature information we have mentioned and our predictions.

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