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Original Research Article

The Roles of Serum Levels of IGF-I And IGFBP 3 in Laboratory Diagnosis of Chronic Obstructive Pulmonary Disease

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Abstract

The lung condition known as chronic obstructive pulmonary disease (COPD) is characterized by remodeling non reversibly of the airways, including fibrosis, smooth muscle hyperplasia, and airway inflammation. By interacting with numerous inflammatory mediators and intricate signaling pathways, insulin-like growth factor-I (IGF-I) causes airway remodeling. The form of IGFBPs that is most prevalent is IGFBP-3. IGF-1 is bound by the IGF-1 receptor, IGFBP-3, which prevents IGF-1 from suppressing airway inflammation. IGFBP-3 is crucial in this situation for controlling the inflammatory response. By examining the circulation levels of IGF-1 and IGFBP3 in newly diagnosed and untreated COPD patients, we sought to contribute to the innovative COPD diagnosis and therapy approaches.

Keywords: Airway inflammation, Airway smooth muscle, Chronic obstructive pulmonary disease (COPD), IGF-binding protein 3 (IGFBP3), Insulin-like growth factor I (IGF-I)

INTRODUCTION

Chronic airway inflammation and blockage are features of the extremely common chronic condition known as COPD. The gradual nature of airway blockage in COPD is widely known to be mainly irreversible. The respiratory tract is affected by inflammation with this condition, which also has systemic symptoms (Marin et al., 2011; Nakawah et al., 2013)

In response to hormones released by the pituitary, liver cells primarily create insulin-like growth factors (IGFs) (Yakar et al, 2012; Nurwidya etal. 2013). The synthesis of IGF-I takes place under the control of growth hormone (GH) releasing hormone and ghrelin, and IGF-I secretion is primarily suppressed by itself(Spiess et al., 1983, Kojima et al., 1999, Butler et al., 2001, Brazeau et al., 1973). IGF activity in the metabolism of glucose, lipids, and proteins is around 1% that of insulin. IGFs also encourage myoblastic or osteoblastic tissues to differentiate into muscle and bone (Wang et al., 2013;Trueba-Saiz et al., 2017). In addition, IGF-1 plays a role in various diseases such as cancer other than developmental disorders and metabolic disorders. Expression of IGF-1 signaling components in cells from normal lung tissue, including respiratory tract cells, lung parenchymal cells, smooth muscle cells, lung fibroblasts, and alveolar macrophages, were confirmed by immunological and genetic analysis (Allen et al., 2000; Hazrati et al., 2022). IGF-I modulates inflammatory processes like subepithelial fibrosis, airway inflammation, and smooth muscle hyperplasia through interacting with a variety of inflammatory agents(Lee et al., 2014).

The half-life of approximately 98% of IGF-I in body fluids is dependent on Insulin-like growth factor binding proteins (IGFBPs) (Hwa et al., 1999; Waters et al., 2022). In this respect, IGFBPs are major regulators of the biological action of IGFs. The most prevalent form of IGFBPs, IGF-binding protein 3 (IGFBP3), has a strong affinity for binding to IGF-I. Thus, it may show effects such as suppression of airway inflammation and airway

Table 1. The comparisons of results between the patient and control groups.

GROUPS / Characteristics	COPD (n=35)		Control (n=25)		P values
	Female (n=16)	Male (n=19)	Female (n=11)	Male (n=14)	
IGF-I (ng/ml)	3.48 ± 0.16		1.71 ± 0.20		0.039
IGFBP3 (ng/ml)	0.82 ± 0.05		0.75 ± 0.02		0.15

Data are mean ± SEM.COPD; Chronic obstructive pulmonary disease, IGF-I; Insulin-like growth factor I, IGFBP3; IGF-binding protein 3.

hyper responsiveness(Jogie-Brahim et al, 2009, Domené et al, 2005).

By examining the circulation levels of IGF-1 and IGFBP3 in newly diagnosed and untreated COPD patients, we sought to contribute to the innovative COPD diagnosis and therapy approaches.

MATERIALS AND METHODS

Patients

The Kütahya Health Sciences University, Faculty of Medicine, Department of Chest Disorders, Kütahya, Turkey, handled a total of 60 subjects for this study. The patient group consisted of 35 unrelated COPD patients (19 men, 16 women), whereas the control group consisted of 25 (14 men, 11 women) healthy, age-appropriate individuals (14 men, 11 women). The entire group was chosen from the Turkish population. The suggested criteria from the Global Initiative for Chronic Obstructive Lung Disease used as the foundation for the diagnosis of COPD (GOLD Guideline, 2014). Before giving their written informed consent, each participant received a personalized description of each procedure. The AfyonKocatepe University Ethics Committee accepted the study protocol and determined that it complied with the Declaration of Helsinki's ethical principles.

Enzyme-Linked Immunosorbent Assay (ELISA) Analyses

All individuals provided peripheral blood samples (5 ml) that were collected in tubes without EDTA. To allow the blood to coagulate, they have been left at room temperature for around 15 to 20 minutes. Each participant's collected blood samples were centrifuged for 15 minutes at 3000 rpm to separate the fibrinogen precipitate and produce serum. The serum samples were centrifuged and then kept at -80 °C for ELISA (Enzyme-Linked Immunosorbent Assay) analysis.

InRel Assay Diagnostics Research Laboratories in Turkey, ELISA kits without stimulation were used to measure the serum levels of IGF-I and IGFBP3. An ELISA microplate reader was used to assess the chemiluminescence results (das, Digital and Analog Systems, Vimercate, MI, Italy).

Statistical analyses

The statistical analyses were carried out using the SPSS (Statistical Program for Social Sciences, Chicago, IL, USA) 16.0 package application. Using a two-tailed test, an 80% confidence interval, and an alpha level of 5% significance, the statistical power for the COPD and control groups was computed. Relevant parameters' serum levels were presented as mean ± standard error of the mean (SEM). The Mann-Whitney U test was used to examine the statistically significant differences between the two groups for each parameter of interest. At a p-value of 0.05, differences were deemed significant.

RESULTS

The patient group consisted of 35 unrelated COPD patients (19 men, 16 women), whereas the control group consisted of 25 (14 men, 11 women) healthy, age-appropriate individuals (14 men, 11 women) (Table 1). The control group's average age was 49 (with a range of 40–58) whereas the COPD group's was 53 (with a range of 42 to 63). There were no statistically significant age or gender mean differences between the two groups ($p > 0.05$).

In the COPD group, the mean serum IGF-I level was found to be 3.48± 0.16 ng/ml, compared to 1.71± 0.20 ng/ml in the control group. We found that the COPD group's serum levels of IGF-I were significantly higher compared to the control group ($p = 0.039$) (Table 1) (Fig 1).

The mean serum IGFBP3 level was determined to be 0.75 ± 0.02 ng/ml in the control group and 0.82 ± 0.05 ng/ml in the COPD group. When compared to the control group, the COPD group's serum levels of IGFBP3 were higher, though not statistically significantly ($p = 0.15$) (Table 1) (Figure 1).

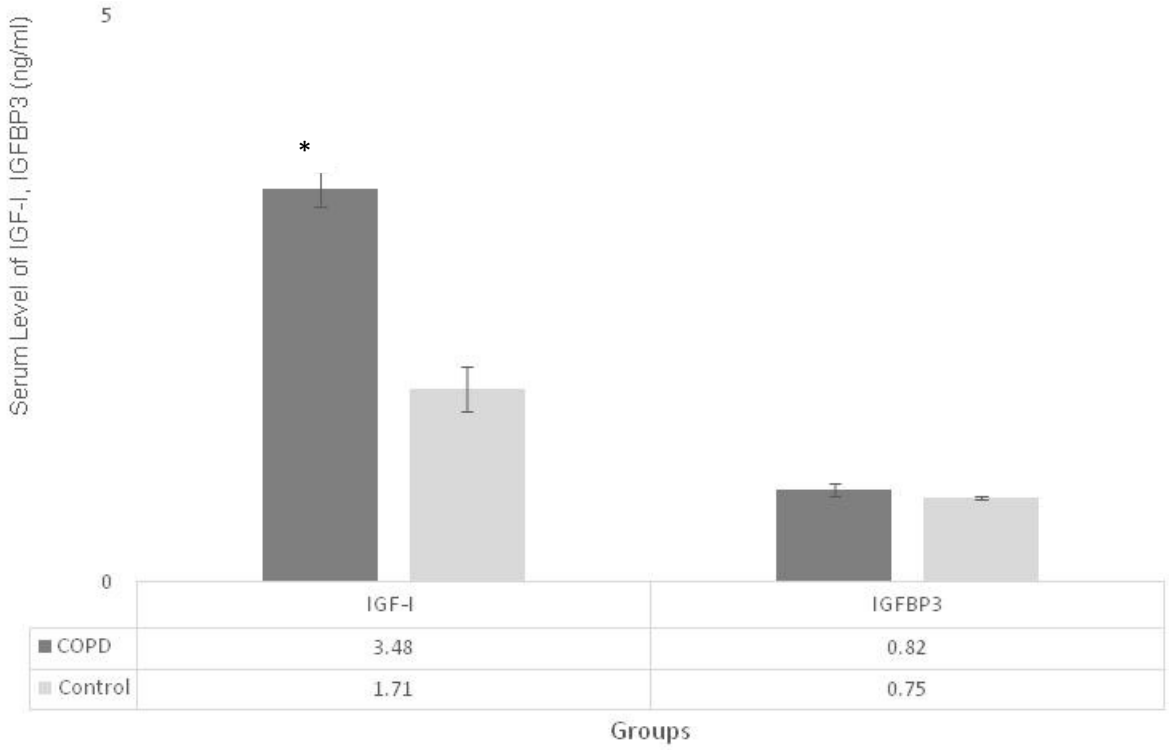

Figure 1. Serum Level of Apelin and Ghrelin in COPD and control groups.
COPD; Chronic obstructive pulmonary disease, IGF-I; Insulin-like growth factor I, IGFBP3; IGF-binding protein 3.
*; $p < 0.05$ vs. control group.

DISCUSSION

Chronic obstructive pulmonary disease (COPD) is a persistent lung inflammation condition which causes fixed airflow restriction and persistent symptoms. The development of the condition and death in COPD are correlated with systemic and pulmonary inflammation (Vogelmeier et al., 2017).Airway inflammation in COPD can affect both the large and small airways (Vogelmeier et al., 2017;Saetta et al., 1998; Di Stefano et al., 1998; George et al., 2016; Scambler et al., 2018; Huber et al., 2023).Various studies have suggested that several processes assumed to be mediated by inflammation may influence the development of COPD (Oudijk et al.,2005; Agustí et al., 2003; Decramer et al., 2012; Morrow et al., 2019). Although airway inflammation plays a significant role in the development and exacerbations of COPD, treatment options focus on symptomatic bron-choconstriction management than anti-inflammatory medication (Vogelmeier et al., 2017).

The neuroendocrine system undergoes changes as part of the physiological response to inflammation, helping the body fight off the aggressor and adapt to the new environment. This neuroendocrine reaction, which is an adaptive or stress response, causes the release of energy substrates from liver, skeletal muscle, and adipose tissue for use by the activated immune system (Straub, 2014).

One of the well-known families of growth factors that have been shown to have a significant role in regulating cell development and transformation is the insulin-like growth factor (IGF) family (Samani et al.,2007).In response to pituitary hormones, the liver cells primarily create insulin-like growth factors (IGFs), which are then released by the brain in feedback signaling loop between the pituitary, liver, and growth hormone-releasing hormone (Yakar et al., 2012; Nurwidya et al., 2013). IGFs have around 1% of insulin's action when it comes to the metabolism of glucose, lipids, and proteins. IGFs also encourage myoblastic or osteoblastic tissues to differentiate into muscle and bone (Trueba-Saiz et al., 2017). IGF-1 is a metabolic mediator that is also linked to developmental abnormalities, several illnesses outside metabolic disorders, and malignancies. Airway cells, lung parenchymal cells, smooth muscle cells, lung fibroblasts, and alveolar macrophages are among the cells from the normal lung tissue that express IGF-1 signaling components, according to immunological and genetic research (Allen et al., 2000; Hazrati et al., 2022).The previously understood function of IGF-1 signaling in lung development and illnesses, such as congenital abnormalities, malignancies, inflammation, and fibrosis, has been redefined by recent studies (Stiles et al., 1990).

Like other endocrine axes, the hypothalamic-growth

hormone (GH)-IGF-1 axis is influenced by inflammation (Soto et al., 1998). On the other hand, depending on the animal species examined as well as the severity and duration of inflammatory stimuli, the impact of inflammation on pituitary GH production differs (Martín et al., 2021).Findings suggest that GH secretion is inhibited in rats and humans with chronic inflammatory disorders (Soto et al., 1998; Lopez-Calderon et al., 1999; Neidhart et al., 1992; Cirillo et al., 2018; Maleta et al., 2021; Van den Berghe et al., 1998).

Except for one study, which demonstrates that circulation levels of IGF-1 in patients with stable COPD are comparable to control levels, abnormal IGF-1 signaling is evident in most investigations (Piehl-Aulin et al., 2009).Thus, circulating GH or IGF-I concentrations in COPD are poorly understood (Scalvini et al., 1996). When compared to patients with stable stage COPD, individuals hospitalized for acute exacerbations of COPD (AECOPD) have considerably lower blood levels of IGF-1 (Ye et al., 2012; Kythreotis et al., 2009; Corbo et al., 2014).As patients are discharged, the blood levels of IGF-1 dramatically rise, however AECOPD patients' serum levels of IGF-1 are lower than those of healthy controls both at admission and discharge (Kythreotis et al., 2009; Corbo et al., 2014). Both at admission and after discharge, emphysematous patients appear to have much lower IGF-1 levels than chronic bronchitis patients (Kythreotis et al., 2009). These findings suggest that systemic inflammation may decrease circulating IGF-1 levels in COPD patients, especially during acute exacerbations. Persistent systemic inflammation, in conjunction with endocrine disorder, can result in anabolic dysfunction and may play a role in muscle wasting and weight loss (Ye et al., 2012).

In our study, we observed that the serum IGF-I levels of newly diagnosed COPD patients increased significantly compared to normal individuals. As we mentioned, there is no correlation between serum IGF-I and IGFBP3 levels in serum COPD patients in the literature. The decreased serum IGF-I level in AECOPD has been associated with GH suppressed by inflammation. Presented as an increase in serum IGF-I level was detected in COPD patients who responded positively to treatment. In the light of this information, we think that the increase observed in serum IGF-1 levels in newly diagnosed COPD patients may be a serum parameter that should be considered in the diagnosis of COPD. IGF-I, which may play a role in the pathogenesis of COPD disease, have also had a genetic polymorphism. For this reason, we think that it would be more appropriate to evaluate the differences in IGF-I levels in COPD patients from different populations at the same time in terms of polymorphism. In addition, the issue that we need to mention is that to prevent recurrent hospitalizations of COPD patients, current treatment methods should be developed with new strategies, considering serum IGF-I levels.

The seven proteins known as IGF-binding proteins (IGFBPs) bind the two IGFs. The liver produces IGFBP-1, 2, 3, and 5, which are then released into the plasma. IGFBP-3 is one of the essential proteins in the IGF-1-IGFBPs system since it is the most prevalent and the primary carrier of IGF-1 in plasma among these proteins. IGF-1 bioavailability is lowered by IGFBP-3 binding to IGF-1 in plasma. The IGF-1 half-life is, however, considerably lengthened by circulating IGFBP-3 (Allard et al., 2018).Moreover, there are several IGF-1 independent effects that local IGFBP-3 can have on cells (Varma Shrivastav et al., 2020).

We could not find a study in the literature comparing serum IGFPB3 levels in newly diagnosed COPD patients with normal individuals. In our study, we detected insignificantly increased serum IGFP3 levels in COPD patients compared to normal individuals. It has been reported in the literature that the increase in serum IGFPB3 level is caused by increased IGF-I (DiGirolamo et al., 2000; Conover et al., 1995). We think that this increase observed in COPD patients is related to increased IGF-I levels. It has been reported that IGFBP3 is also involved in the pathophysiology of asthma in an IGF-I-independent and IGF-I-dependent manner. Therefore, it is suggested that increasing IGFBP3 gene expression may be one of the new strategies in the treatment of asthma (Lee et al. 2014). We also believe that the increase in serum IGFBP3 level due to IGF-I may play a role in the pathophysiology of COPD. In the light of this information, we think that targeting IGFBP3 in the development of new treatment strategies may be beneficial in the development of new and effective treatment methods in COPD, especially by suppressing the inflammatory effects of IGF-I. As with IGF-I, genetic differences can be observed between populations in IGFBP3. We advocate that this situation should be taken into consideration in the evaluation of the treatment of patients. In addition, we would like to point out that the genetic differences of IGF-I and IGFBP3 are still an issue that needs to be explained for COPD.

CONCLUSION

COPD is still a disease that is difficult to diagnose and treat, and there are many gaps that need to be clarified. In our study, we tried to explain the role of serum levels of IGF-I and IGFBP3 in the laboratory diagnosis of COPD. We predict that the increase in IGF-I levels may be a parameter that should be emphasized in the diagnosis of COPD, since our patients must have been newly diagnosed and did not use any medication for treatment. In addition, it is known that the related parameters may show genetically polymorphic features among populations. Therefore, we can say that there is a need for new studies in which IGF-I and IGFBP3 in COPD are compared with genetically different

populations and patient parameters. We think that the data we obtained and our literature discussion will contribute to the literature for future studies.

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