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Original Article

Visfatin and ghrelin: can they be forthcoming biomarkers or new drug targets for asthma?

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Abstract: Background & aim: Asthma represents chronic inflammation of the airways and is associated with bronchial hyperresponsiveness and reversible airway obstruction. A novel adipokine visfatin and an appetite-modulating hormone ghrelin play a role in several diseases related with inflammation. Although visfatin is a pro-inflammatory adipokine, ghrelin mainly exerts anti-inflammatory effects. However, very little is known about the role of visfatin and ghrelin in asthma. In the present study, we aimed to investigate the role of visfatin and ghrelin in asthma by evaluating their serum levels in asthmatic patients. Materials and methods: This study was performed on 27 asthma and 23 healthy controls. Blood samples were collected in tubes without EDTA. Serum levels of visfatin and ghrelin were measured by human ELISA assay kits. Statistical analyses were performed by SPSS 16.0 package program and differences were considered statistically significant at $p < 0.05$. Results: Serum levels of visfatin and ghrelin were significantly higher in asthma group (respectively; $p = 0.001$, $p = 0.002$). Conclusion: While visfatin has a pro-inflammatory role, ghrelin exerts an anti-inflammatory effect in asthma. Therefore, visfatin can be a forthcoming biomarker and ghrelin may be a new anti-inflammatory drug target to diagnose and treat asthmatic patients.

Keywords: Asthma, inflammation, visfatin, adipokine, ghrelin, appetite-modulating hormone, biomarker, drug target

Introduction

Bronchial asthma is a chronic inflammatory lung disease which is characterized by airway inflammation, reversible airway obstruction and airway hyperresponsiveness [1]. However, chronic inflammation in asthma is not only limited to lungs, it has both pulmonary and systemic features [2].

Adipokines are protein mediators secreted by adipose tissue. They play role both in the regulation of energy metabolism and inflammatory responses of many chronic inflammatory diseases [3, 4]. Also, adipokines have also been linked to inflammatory lung diseases such as asthma [5].

Visfatin is a pro-inflammatory adipokine which is also known as nicotinamide phosphoribosyl transferase (NAMPT) [6, 7]. It is mainly expressed and secreted by adipose tissue and is involved in the regulation of inflammation [6, 8].

Ghrelin is a 28-amino-acid peptide predominantly produced by the stomach [9]. As a gastric hormone ghrelin increases appetite and plays a role in the long-term regulation of energy metabolism and short-term regulation of feeding [10, 11]. It modulates the release of pro-inflammatory cytokines and exerts anti-inflammatory effects [12].

However, studies about the potential role of ghrelin and a novel adipokine-visfatin in asthma are lacking. That is why we aimed to evaluate

Table 1. Age and gender distribution of the groups

	Asthma group (n = 27)	Control group (n = 23)
Female	23	19
Male	4	4
Age (years)	39.3 ± 2.7	45.0 ± 4.2

the role of ghrelin and visfatin in asthmatic patients.

Materials and methods

Patients

This was a prospective study which was carried out between July 2013 and December 2013. The study group consisted of 27 patients with asthma and 23 healthy age-gender-matched controls. The patients who were diagnosed and treated as asthma according to the 2013 Global Initiative for Asthma (GINA) Guideline and on clinical follow-up at Dumlupınar University Medical Faculty, Department of Chest Diseases and Yedikule Chest Diseases & Thoracic Surgery Training & Research Hospital, Department of Chest Diseases were involved in our study. Ethical approval of this study was received from Abant İzzet Baysal University Clinical Research Ethical Committee and written informed consent forms were taken from the study participants.

ELISA analyses

Peripheral blood samples were collected in tubes without EDTA from all subjects. After centrifugation, serum of each individual was stored at -80°C until ELISA analysis. Serum concentrations of visfatin (Cusabio Biotech, Cat No CSB-E08940h) and ghrelin (Cusabio Biotech, Cat No CSB-E13398h) were analyzed by rat ELISA assay kits. Chemiluminescence data were analyzed by an ELISA microplate reader (das, Digital and Analog Systems, Vimercate, MI, Italy).

Statistical analyses

Statistical analyses were performed by SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) 16.0 package program. Serum levels of interested parameters, age and BMIs were given as mean ± standard error of the mean (SEM). Statistical significances between two groups were analyzed by Mann-Whitney U tests. Differences were considered significant at $p < 0.05$.

Results

The asthma group was consisted of 23 female and 4 male (n = 27) and control group was consisted of 19 female and 4 male (n = 23). Mean age was found as 39.3 ± 2.7 in asthma and 45.0 ± 4.2 in the control group. Age and gender distribution of the groups is shown in **Table 1**.

Body mass index (BMI) of asthma and control groups were 28.3 ± 1.16 kg/m^2 and 24.9 ± 1.13 kg/m^2 respectively. Statistically significant difference was observed between groups in means of BMI (p = 0.015) (**Table 2**). Serum level of visfatin was found as 0.093 ± 0.01 pg/ml in asthma and 0.046 ± 0.007 pg/ml in control group. Serum level of ghrelin was detected as 125.9 ± 3.18 pg/ml in asthma and 114.1 ± 3.07 pg/ml in control group. Statistically significant differences were observed between groups for serum levels of visfatin and ghrelin (respectively; p = 0.001, p = 0.002). Serum levels of visfatin and ghrelin were significantly higher in asthma group (**Table 2**).

Discussion

Bronchial asthma is a chronic inflammatory disorder of the airways in which chronic inflammation is associated with airway hyperresponsiveness and variable airflow obstruction that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing [13].

Adipose tissue is metabolically active and is in filtrated by bone-marrow derived macrophages. These macrophages are an important source of inflammation in adipose tissue because they secrete adipokines and cyto-kines in the systemic circulation which results in a chronic inflammatory state [14, 15]. Therefore, the increase in adipose tissue is associated with increased levels of circulating cytokines including tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 which are important in the induction of inflammatory responses and the spread of inflammation in the pathogenesis of several diseases [3, 16, 17]. Additionally, IL-1 beta (IL-1β) and TNF-α are the two inducers of IL-6 which were mainly produced by the lungs [18]. Today we know that IL-1β, TNF-α and IL-6 are the key mediators involved in the pathogenesis of asthma.

Table 2. BMIs, serum levels of visfatin and ghrelin and *p* values in asthma and control groups

	Asthma group (n = 27)	Control group (n = 23)	*p*
BMI (kg/m^2)	28.3 ± 1.16	24.9 ± 1.13	0.015*
Serum level of visfatin (pg/ml)	0.093 ± 0.01	0.046 ± 0.007	0.001***
Serum level of ghrelin (pg/ml)	125.9 ± 3.18	114.1 ± 3.07	0.002***

*$p < 0.05$ shows the significant differences between groups (Mann-Whitney U test). ***$p < 0.005$ shows the significant differences between groups (Mann-Whitney Utest).

Increasing adiposity has been identified as a risk factor for the development of asthma [19]. Forwhy, adiposity contributes to the pro-inflammatory domain and is responsible for the formation of chronic low-grade inflammation [20]. It is reported that there is a dose response relationship between BMI and asthma, suggesting that asthma risk is increasing with elevated body weight [21]. Additionally, Schachter et al. demonstrated that the symptoms of asthma increased with a rise in BMI [22]. Beuther et al. reported that those overweight (BMI 25-29.9 kg/m^2) individuals were more likely to develop asthma compared to those with normal weight [21]. In our study, patients with asthma have higher BMI than control group. As the participants with asthma were overweight compared to controls, our findings suggest that overweight individuals with increased BMI are more at risk of developing asthma compared to the individuals with normal weight. In this regard, our findings were consistent with literature.

Adipokines, factors produced by adipose tissue, were found to be associated with chronic low-grade inflammation in inflammatory lung diseases like asthma and COPD [23-25]. Some adipokines have pro-inflammatory properties and effects of these adipokines on lungs have the potential to evoke or exacerbate asthma [23].

Visfatin, also known as NAMPT, is described as a new adipokine in 2005 and its secretion from adipose tissue was shown [7, 26]. Visfatin is one of the pro-inflammatory adipokines which was originally discovered in lymphocytes, bone marrow, liver, muscle and subsequently identified in the lungs [4, 7, 27]. It is known that visfatin is involved in inflammation and upregulation of this adipokine leads to the development of a chronic low-grade inflammatory state [4, 28].

In a study by Machura et al., it has been reported that serum level of visfatin was lower in school children with atopic asthma. They suggested that there is not a relationship between visfatin level and asthma so that visfatin is not a potential biomarker for childhood atopic asthma [29]. In another study, Leivo-Korpela et al. suggested that visfatin is a novel inflammatory factor in COPD because of its pro-inflammatory role in the pathogenesis of this disease [30]. Today, we know that asthma is similar to COPD in terms of chronic airway inflammation [31]. Magrone et al. found that serum level of visfatin was elevated with the increase in BMI values of asthmatic children [32]. In a study by Moschen et al., it was shown that visfatin leads to the production of pro-inflammatory cytokines such as IL-1β, TNF-α and IL-6 which was suggesting the pro-inflammatory role of visfatin [6]. In our study, an increase in serum level of visfatin was observed in asthmatic patients. As because visfatin is an adipokine we think that the increase of visfatin is most probably related with the increased adiposity in these individuals. Additionally, we suggest that visfatin may play a pro-inflammatory role in the development of asthma by the release of pro-inflammatory cytokines that are involved in the pathogenesis of this disease.

Ghrelin is an appetite modulating hormone which increases food intake and body weight. It has adipogenic, orexigenic, and somatotropic properties [10]. Ghrelin exerts anti-inflammatory actions through the inhibition of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6, which are involved in the pathogenesis of asthma [33]. Tsaroucha et al. assessed the circulating concentrations of ghrelin in asthmatic patients and they reported that ghrelin concentrations were significantly lower in asthmatic patients compared to controls [34]. Matsumoto et al. found that the level of ghrelin tended to be lower in the asthmatics than in non-asthmatic individuals [31]. In a study by Yuksel et al., it was reported that the serum levels of ghrelin were decreased in asthmatic children and they suggested that ghrelin has an anti-inflammatory role in the pathogenesis of asthma by competing against IL-6 and TNF-α [35]. In contrast to these studies, we have observed

a significant increase in the serum level of ghrelin in asthmatic patients. At this point, we would like to draw attention to the anti-inflammatory effect of ghrelin which may have a noteworthy role in asthma. We hypothesize that this increase in ghrelin may be associated with its inhibitory role on pro-inflammatory cytokines. Because in parallel to the increase of pro-inflammatory cytokines in asthma, an increase in the level of ghrelin is expected to demonstrate its inhibitory effect on these cytokines. We know that it would be better to evaluate serum levels of IL-1β, TNF-α and IL-6 and search their correlation with serum levels of visfatin and ghrelin in order to support our hypothesis. However, we could not perform this step which is a limitation of our study. On the other hand, this is the first study reporting the serum levels of both visfatin and ghrelin in adult asthmatic population.

Upon our results, we can conclude that visfatin has a pro-inflammatory role while ghrelin acts through its anti-inflammatory effects in the development of asthma. Finally, we suggest that visfatin can be used as a novel biomarker in the diagnosis of asthmatic patients and ghrelin may be a new anti-inflammatory drug target to treat these patients in the near future. However, we believe that further studies are needed to clarify our results.

Conclusion

Although visfatin plays a pro-inflammatory role, ghrelin exerts an anti-inflammatory effect in asthma. Visfatin can be a forthcoming biomarker and ghrelin may be a new anti-inflammatory drug target to diagnose and treat patients with asthma.

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Disclosure of conflict of interest

None

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