

Evaluation of Interleukin-6, Leukotriene B-4, and Nitric Oxide Levels in Exhaled Breath Condensate of Asymptomatic Obese Individuals: Are Obese Patients Under Risk of Developing Asthma?

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ABSTRACT

Objective: If systemic inflammation in relation with obesity causes asthma, the detection of increased airway inflammation among obese individuals who do not have any respiratory symptoms can be also beneficial in identifying obese patients who are at risk of developing asthma. The aim of this study was to evaluate the systemic and airway inflammation of asymptomatic obese and non-obese individuals.

Materials and Methods: Obese and non-obese individuals with no respiratory symptoms were included. Inflammatory biomarkers such as C-reactive protein (CRP), exhaled breath condensate (EBC) interleukin-6 (IL-6), EBC leukotriene B-4 (LTB-4), and EBC nitric oxide (NO) levels of obese and non-obese individuals were determined.

Results: Forty-five obese individuals (body mass index [BMI] ≥ 30) and 31 non-obese individuals (BMI ≤ 25) as a control group were included in this study. The mean age of the obese group (38.7 ± 11.4 years) was significantly higher than the one of the non-obese group (29.5 ± 8.6 years; $p < 0.001$). There was no significant relationship between gender and BMI ($\chi^2 = 1.471$, $p = 0.225$). CRP levels were significantly higher in the obese group (6.94 ± 8.28) than the non-obese group (3.29 ± 0.39 ; $p < 0.001$). The levels of EBC IL-6 in obese and non-obese group were found as 22.61 ± 12.53 and 21.08 ± 14.39 , respectively ($p = 0.624$). There was no significant difference between EBC NO levels of the obese group and non-obese group (24.35 ± 10.9 vs. 21.56 ± 7.83 ; $p = 0.226$). No significant difference was found between the EBC LTB-4 level in the obese group and the non-obese group (36.39 ± 89.82 vs. 16.64 ± 17.45 ; $p = 0.231$).

Conclusion: Increased systemic inflammation in obese individuals who had no respiratory symptoms might indicate the tendency of asthma. However, airway inflammation was not significantly different between groups. Therefore the relationship between obesity and asthma should be investigated in future large-scale studies determining the direct effects of adipokines on airways.

Keywords: Obesity, airway inflammation, systemic inflammation

Introduction

Obesity is an increasing global public health problem [1]. The prevalence of asthma keeps increasing in obese individuals, and over 75% of the people who are consulted in emergency room with severe asthma are obese or overweight [2-6]. The simultaneous increase in asthma and obesity prevalence and asthma-like symptoms in obese individuals make researchers think that there may be a link and common pathogenesis between two conditions.

The relation between obesity and asthma is tried to be explained by mechanical and inflammatory theories [7]. According to inflammatory theory, the proinflammatory adipokines excreted from the adipose tissue cause both systemic and airway inflammation that leads to asthma [1-3]. Previous studies have shown that interleukin-6 (IL-6) and leukotriene B-4 (LTB-4) are associated with the allergic pathogenesis of asthma and allergic diseases [8].

If systemic inflammation due to obesity causes asthma, the detection of airway inflammation in asymptomatic obese individuals would be useful in identifying obese patients who are at risk of developing asthma. Accordingly, the aim of the present study was to investigate inflammatory markers such as serum C-reactive protein (CRP) and exhaled breath condensate levels of IL-6, LTB-4, and nitric oxide (NO) in obese and non-obese individuals with no respiratory

symptoms, to determine systemic and airway inflammation.

Materials And Methods

Study Population

A total of 45 obese individuals (body mass index [BMI] ≥ 30 kg/m²) 36 females, 9 males) and 31 non-obese individuals (21 females, 10 males) without respiratory symptoms were included in this study. Subjects aged <18 or >60 years were excluded. The subjects with the diagnosis of airway disease by a physician and were initiated inhaler treatment, receiving immunosuppressant treatment due to any disease (steroid, hormone replacement, statin); with diabetes mellitus, systemic hypertension, congestive heart failure, chronic kidney failure, inflammatory bowel disease, rheumatoid arthritis, scleroderma, and other collagen vascular diseases; subjects who had upper or lower respiratory tract infection within last month, subjects with gastroesophageal reflux symptoms; history of allergies and obstructive sleep apnea (OSA) symptoms were excluded from the present study. Berlin questionnaire (BQ) was performed to exclude the OSA co-existence [9]. According to BQ, the subjects with medium and high-risk OSA syndrome were not included in this study. Pulmonary function tests according to the American Thoracic Society and European Respiratory Society standards [10] and skin prick test [11] were performed to all cases. The subjects who had airflow limi-

tation and positive skin prick test results were not included in this study. The current study protocol was approved by the Local Ethics Committee (2012/31). Informed consent was obtained from the participants.

Collection of exhaled breath condensate

Breath was gathered from subjects using an electric refrigerated system modified from a cold air challenge device (EcoScreen, Hoechst, Germany). Subjects sat upright on a chair, wore a nose clip, and exhaled into a cooled chamber at the tidal volume throughout the 5–15 minute collection period. Device had a salivary trap consisting of a hole near the mouthpiece that reportedly keeps the collected fluid amylase free. The liquid condensed from breath was put in Eppendorf tubes and was sent to the laboratory in dry ice immediately. The samples were kept at -80°C till the analysis.

Serum C-Reactive Protein Measurement

All serum samples of the patients were examined in Gaziosmanpasa University School of Medicine, Microbiology Laboratory by using CRP hs CardioPhase kit in NBI device with the ELISA method.

NO, IL-6, LTB-4 Measurement in Exhaled Breath Condensate

NO in EBC (Cayman Chemical Company, MI, USA) (Item no: 780001) were measured via colorimetric method, LTB-4 (LTB-4 EIA kit, Cayman Chemical Company, MI, USA, [Item no:520111]) were measured via the competitive enzyme immuno assay (EIA) method, IL-6 (AviBion Human IL-6 ELISA Kit (Origenium Laboratories, Vantaa, FINLAND)(Ref No: IL06001) levels were measured with the ELISA method.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences statistics version 20 (IBM Corp.; Armonk, NY, USA).

The distribution of continuous variables used in this study was evaluated using the Levene test. Comparison of continuous variables showed normal distribution within two groups was performed with independent samples t-test; comparison of continuous variables that did not show normal distribution within two groups was performed using the Mann–Whitney U test. Continuous variables were expressed as the mean and standard deviation. In comparison of two groups regarding gender, the chi-squared test was used. Categorical variables were expressed as numbers and percentages. A $p < 0.05$ was accepted as statistically meaningful.

Results

Forty-five obese (BMI ≥ 30 kg/m²) and 31 non-obese (BMI ≤ 25 kg/m²) subjects as a control group were enrolled in the present study. The mean age of the obese group (38.7 ± 11.4 years) was significantly higher than the mean age of the non-obese group (29.5 ± 8.6 years) ($p < 0.001$). 80% of obese subjects and 67% of non-obese subjects were female. No significant relation was detected between BMI and gender ($\chi^2 = 1.471$, $p = 0.225$). The distribution of gender is demonstrated in Table 1.

Serum CRP levels in obese subjects (6.94 ± 8.28) were significantly higher than in non-obese subjects (3.29 ± 0.39) ($p < 0.001$). IL-6 levels in EBC were detected as 22.61 ± 12.53 in obese subjects and 21.08 ± 14.39 in non-obese subjects, and no statistically significant difference was detected between the groups ($p = 0.624$). NO levels in EBC were detected as 24.35 ± 10.9 in obese subjects, and 21.56 ± 7.83 in non-obese subjects ($p = 0.226$). LTB-4 levels in EBC were 36.39 ± 89.82 in obese subjects and 16.64 ± 17.45 in non-obese subjects ($p = 0.231$). Comparison of IL-6, LTB-4, and NO in EBC and serum CRP values between obese and non-obese subjects is shown in Table 2.

Table 1. Distribution of gender between obese and non-obese subjects

	Male N, (%)	Female N, (%)	Total N, (%)
BMI ≤ 25 kg/m ²	10 (32.3)	21 (67.7)	31 (100)
BMI ≥ 30 kg/m ²	9 (20)	36 (80)	45 (100)
TOTAL	19 (25)	57 (75)	76 (100)

BMI: Body mass index

Table 2. Comparison of EBC IL-6, LTB-4, and NO levels and serum CRP values between obese and non-obese subjects

Variables	Non-obese Subjects (n=31)					Obese Subjects (n=45)					p
	n	$\bar{x}$	SD	SE	95% Confidence Interval	n	$\bar{x}$	SD	SE	95% Confidence Interval	
Age	31	29.52	8.64	1.55	(26.35-32.68)	45	38.69	11.40	1.70	(35.25-42.11)	<0.001**
BMI	31	22.61	1.82	0.33	(21.95-23.28)	45	36.58	7.44	1.11	(34.34-38.81)	<0.001**
Serum CRP levels	31	3.29	0.39	0.07	(3.15-3.43)	45	6.94	8.28	1.23	(4.46-9.43)	<0.001**
EBC IL-6 levels	31	21.08	14.39	2.59	(15.79-26.36)	45	22.61	12.53	1.87	(18.85-26.37)	0.624*
EBC LTB-4 levels	31	16.64	17.45	3.13	(10.24-23.04)	45	36.39	89.82	13.39	(9.41-63.37)	0.231*
EBC NO levels	31	21.56	7.83	1.41	(18.69-24.44)	45	24.35	10.90	1.63	(21.08-27.63)	0.226*

BMI: Body mass index; CRP: C-reactive protein; EBC: Exhaled breath condensate; IL-6: Interleukin-6; LTB-4: Leukotriene B-4; NO: Nitric oxide, mean; SD, standard deviation; SE, standard error

* Independent group t-test

** The Mann–Whitney U test was used.

Discussion

In the present study, serum CRP levels were found to be higher in obese subjects than in non-obese subjects; however, EBC IL-6, LTB-4, and NO levels were found to be similar in obese and non-obese subjects.

The serum CRP level is a reliable parameter used as a systemic inflammation indicator. The serum CRP level in individuals who have normal liver functions show inflammatory activation. The concentration in serum are related to IL-6 and TNF- α levels [12]. CRP levels increase in systemic inflammation based on obesity. In the literature, previous studies demonstrated the increased CRP levels in obese individuals as the systemic inflammation indicator similar to the present study. Festa et al. [13] studied the relation between the adipose tissue and inflammation bioindicator in 1559 subjects demonstrating the relationship between BMI and the CRP level. Saijo et al. [14] found the relationship between obesity and serum CRP levels in 116 Asians. In the study by Sutherland et al. [15], CRP levels of obese individuals with asthma were significantly higher than those in non-obese individuals with asthma. In the present study, serum CRP levels of obese subjects without comorbidities were higher than serum CRP levels of non-obese subjects ($p < 0.001$). The result of the present study is consistent with other previous studies reflecting the systemic inflammation in obese subjects.

Inducible nitric oxide synthase (iNOS) produces nitric oxide (NO) from L-arginine in response to inflammatory stimuli. Concerning the bronchus biopsy of individuals with asthma, it is seen that in the areas with inflammation, there is iNOS expression on epithelium [16]. While measuring the airway inflammation, detecting the levels of the mediators excreted from inflammatory cells is used. In individuals with asthma, eosinophilic inflammation plays an important role in airway inflammation. There is research indicating the increased NO levels of the airways in eosinophilic inflammation. In mucus and biopsy samples, it is observed that there is a strong relation between eosinophilic inflammation and EBC NO levels [17]. Sutherland et al. [18] included 79 obese individuals with asthma ($n=20$), non-obese individuals with asthma ($n=19$), obese without asthma ($n=20$), non-obese without asthma ($n=20$) in their study, and they evaluated mucus cell count and the NO level in condensed breath. They demonstrated a significantly increased EBC NO level in patients with asthma when compared to subjects without asthma. However the mucus eosinophil cell count was not significantly different between subjects with and without asthma. IL-4, IL-6, CRP, and leptin

levels were higher in the obese group than in the non-obese group concerning the study of inflammatory bioindicator in the serum and mucus. Leptin is a hormone derived from the adipose tissue, and it provides the feedback about adiposity to the central nervous system. As the adiposity increases, leptin levels decrease the food intake and increase energy expenditure [19]. CRP levels were higher in the subjects with asthma than in subjects without asthma. Biomarkers were not increased in obese individuals without asthma. Finally no relationship was found between systemic inflammation based on obesity and airway inflammation [18]. Leung et al. [15] studied the relation between obesity and airway inflammation, and they included 93 children with asthma and 23 children without asthma. Twenty-two individuals with asthma were obese, and the NO level in the condensed breath of children with asthma was significantly different than in children without asthma, but no difference was observed between obese children with asthma and non-obese children with asthma in terms of EBC NO levels. Farah et al. [20] demonstrated that the asthma control was independent from inflammation and mechanical effects and became harder in obese individuals with asthma. In the study carried out with 49 patients, a 3-month-long high-dose steroid inhaler treatment was initiated, and a control test was performed before and after the treatment. The EBC NO levels were measured, and no difference was observed between obese individuals with asthma and non-obese individuals in terms of EBC NO levels. Mc Lahlan et al. [21] compared the airway inflammation and airway obstruction between obese and non-obese individuals. Breath questionnaire was performed to the patients, bronchodilator sensitivity was evaluated, pulmonary function tests were done, and EBC NO levels were measured. The EBC NO level as an indicator of airway inflammation were not significantly different between obese and non-obese individuals [21]. Kattan et al. [22] included 386 adolescents during 1-year follow up, and the NO level in EBC was checked every 6 weeks, and the serum eosinophil count, adipokines, TNF- α , IL-6, leptin, and CRP levels were measured. There was no relationship between adiposity or adipokines and blood eosinophil counts and the exhaled NO level, and it has been thought that the airway inflammation in obese individuals can be independent from eosinophilic inflammation. In our study, when obese and non-obese subjects were compared, no significant difference was seen in the EBC NO levels ($p=0.226$). This finding is consistent with the previous studies. It is stated in many studies that the level of NO shows eosinophilic inflammation. If we considered that there is no

difference between NO levels, it can be thought that the airway inflammation observed in asymptomatic obese individuals can emerge with mechanisms that are independent from eosinophils.

LTB-4 is a proinflammatory mediator playing important roles in adhesion, migration, and chemotaxis of the leucocytes. Neutrophilic inflammation can also be seen in asthma, especially in cases with severe asthma and difficult-to-treat asthma [23, 24]. Bronchial lavage and endobronchial and transbronchial biopsy results of 14 severe asthma patients were compared with lavage and endobronchial and transbronchial biopsy studies in normal controls and patients with moderate asthma in the study by Wenzel et al. [25]. Severe asthmatics demonstrated a two times higher concentration of neutrophils in lavage than either the mild-moderate asthmatics or the normal controls, and the LTB-4 level as an indicator of neutrophilic inflammation of these severe asthmatic patients was found to be higher [25]. Neutrophilic inflammation should be kept in mind in patients with difficult-to-treat asthma who are obese. Leung et al. [15] included 93 children with asthma and 23 children without asthma in their study, and they examined the relation between obesity and airway inflammation. Twenty-two of the patients with asthma were classified as obese. The LTB-4 level in EBC was significantly different between the children with asthma and without asthma, although there was no statistically significant difference between obese and non-obese children with asthma. In our study, the LTB-4 level in EBC was examined, and no statistically significant difference was detected between obese and non-obese subjects ($p=0.231$). In the light of these findings, it can be thought that airway inflammation in asymptomatic obese individuals can occur with mechanisms independently from neutrophilic inflammation.

IL-6 is a proinflammatory cytokine excreted from many cells [26]. The expression of IL-6 is stimulated via beta-2 and beta-3 adrenergic receptors in adipose cells by catecholamines [27]. In previous studies, serum IL-6 levels were found to be higher in obese subjects. Serum IL-6 levels were found to be correlated with BMI in the study by Rexrode et al. [28]. In another study, Park et al. found out the relationships between all indexes of obesity with IL-6 [29]. Cartier et al. [30] showed the relation of IL-6 with visceral adipocytes. Sutherland et al. found that the IL-6 level of obese individuals with asthma was significantly higher than in non-obese individuals without asthma. Moreover the role of IL-6 excreted from Th2 cells during airway inflammation and the other mediators are also known [31]. The EBC IL-6 level is another

parameter while evaluating the relation between airway inflammation and systemic inflammation in obesity. In our study, no statistically significant difference was detected between the EBC IL-6 level of obese and non-obese subjects ($p=0.624$). This result of the present study is the first preliminary result in the literature, according to our knowledge. Further studies are needed to understand the possible role of IL-6 in airway inflammation of obese individuals.

Although there are studies that show an increased asthma incidence with obesity, the relationship between obesity and airway inflammation is unclear. Despite the hypothesis that obesity causes airway inflammation in the literature, there are some studies those do not support this hypothesis. In this study, different from the previous ones, obese and non-obese subjects without asthma and respiratory symptoms are evaluated to determine airway inflammation in obese subjects. However airway inflammatory markers were not significantly different between obese and non-obese subjects. Therefore, other possible mechanisms should be identified to determine the risk of asthma development.

There are some important drawbacks to this study. First, the lack of a group comprising asthma patients is one of limitations. Second, a small sample size is another limitation. The third limitation is the lack of evaluation of pulmonary function tests. Finally, this study did not exclude the presence of depression. Obesity is associated with depression [32]. It is well known that depression is associated with increased interleukin 6, and depression could be a confounding factor [33].

In conclusion, more detailed and large-scale studies are required that would consider the genetic factors, which are important in the asthma-obesity relation, and examine the direct effects of adipokines excreted from adipose cells on the airway independent from inflammation.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziosmanpaşa University School of Medicine.

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

Peer-review: Externally peer-reviewed.

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