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Effects of Obesity on Airway and Systemic Inflammation in Asthmatic Children

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Keywords
Adiponectin · Airway inflammation · Asthma · Childhood · Obesity · Systemic inflammation

Abstract
Background: Obese asthma is a complex syndrome with certain phenotypes that differ in children and adults. There is no clear evidence regarding the presence of additive or synergistic pathological interaction between obesity and asthma in children. ***Objectives:*** Our aim was to demonstrate the interaction of obesity and asthma in children in terms of airway and systemic inflammation by a controlled observational study. ***Methods:*** Four groups were formed: asthma obese (AO), asthma nonobese (ANO), non-AO (NAO), non-asthma nonobese (NANO). Spirometry test, fractional exhaled nitric oxide (FeNO) test, skin prick test, serum inflammatory biomarkers (C-reactive protein, C3, C4, adiponectin, leptin, resistin, periostin, YKL-40, Type 1, and Type 2 cytokines) were conducted and evaluated in all participants. Sputum inflammatory cells (sputum eosinophils and neutrophils) were evaluated in patients who could produce induced sputum and obesity-asthma interactions were determined. ***Results:*** A total of 153 participants aged 6–18 years were included in the study, including the AO group ($n = 46$), the ANO group ($n = 45$), the NAO group ($n = 30$), and the NANO group ($n = 32$). IL-4 ($p < 0.001$), IL-5 ($p < 0.001$), IL-13 ($p < 0.001$), resistin ($p < 0.001$), and YKL-40 ($p < 0.001$) levels were higher in patients with asthma independent of obesity. The lowest adiponectin level was found in the AO group and obesity-asthma interaction was detected ($p < 0.001$). Sputum eosinophilia ($p < 0.01$), sputum neutrophilia ($p < 0.01$), and FeNO levels ($p = 0.07$) were higher in asthmatic patients independent of obesity. In the group with paucigranulocytic inflammation, resistin and YKL-40 levels were significantly lower than in the group without paucigranulo-

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cytic inflammation ($p < 0.01$). ***Conclusion:*** No interaction was found between obesity and asthma in terms of airway inflammation. Interaction between obesity and asthma was shown in terms of adiponectin level and resistin/adiponectin and leptin/adiponectin ratios. It was found that serum YKL-40 and resistin levels could be associated with airway inflammation.

Introduction

Obesity is a widespread public health problem [1]. It is an important risk factor for asthma as well as a disease-modifying factor in children and adults. Obese asthma is a complex syndrome with certain phenotypes that differ in children and adults [2]. The mechanisms underlying the relationship between obesity and asthma are not comprehensively understood, and numerous hypotheses have been proposed. The underlying potential mechanisms are common genetic predisposition, nutritional factors, changes in intestinal microbiome, systemic inflammation, metabolic abnormalities, lung anatomy, and other changes in lung functions [2, 3]. By releasing important mediators produced by tissue-resident macrophages and adipocytes, including tumor necrosis factor-a (TNF-a), interleukins and adipokines, adipose tissue, through its endocrine capabilities, communicate with other organs. Obesity creates a pro-inflammatory environment with an increase in adipocyte number as well as volume and leading to production of inflammatory mediators [4, 5]. It has been proposed that this chronic systemic inflammation, characteristic of obesity, contributes to the underlying airway inflammation [6]. Adaptive immune responses tend to shift to Th1 in the presence of obesity in asthma [7].

Cumulatively, these findings suggest that there is an underlying mechanism mediating, at least partially, the relationship between obesity and asthma. We hypothesized that low-grade systemic inflammation manifested in obesity can exacerbate inflammation in asthma, or inflammation in obesity can independently cause different or mixed inflammatory cell phenotypes in the airway. To test these hypotheses, we conducted an observational controlled study to compare systemic and airway inflammation profiles in obese and nonobese individuals with and without asthma.

Methods

Participants

The study population consisted of 4 age- and sex-matched groups including children aged between 6 and 18 years: asthmatic obese (AO), asthmatic nonobese (ANO), non-AO (NAO), and nonasthmatic nonobese (NANO). The groups were recruited consecutively from the admissions to the outpatient clinics of the Departments of Pediatric Allergy (obese and nonobese asthmatics), Pediatric Endocrinology (obese controls), and Pediatrics (nonobese controls). Criteria for inclusion in the study were as follows: ability to undergo respiratory function test, no infection, or systemic steroid therapy in the last 4 weeks, FEV_1 value above 70% in respiratory function test. In addition, for the asthma group, inclusion criteria also included follow-up with diagnosis of asthma for at least 1 year and/or having asthma symptoms for at least 1 year, no chronic disease other than atopic dermatitis and allergic rhinitis; for the nonasthma group, inclusion criteria also included having no chronic diseases except for obesity in the obese group and no history of atopy and wheezing. The Ethical Committee of our hospital approved the study, the parents of all the participants provided written informed consent.

Clinical Assessment

The diagnosis of asthma was made according to the guidelines of the Global Initiative for Asthma. Age- and sex-specific BMI percentiles were calculated according to Neyzi et al. [8] for children between 2 and 18 years of age. Participants with a BMI below the 95th percentile were categorized as "non-obese," and those with a BMI at or above the 95th percentile were categorized as "obese." Patients and controls fulfilling the inclusion criteria were recruited for the study. In the asthma group, asthma control was determined by the asthma control test [9]. Patients who were partly controlled and uncontrolled according to the asthma control test were grouped as poorly controlled. Asthma stability was confirmed, defined as no exacerbation, respiratory tract infection, or oral corticosteroid usage in the past 4 weeks. Asthma severity has been assessed retrospectively from the level of treatment required to control symptoms and exacerbations according to Global Initiative for Asthma [10].

FeNO Measurement, Spirometry, and Skin Prick Test

FeNO was measured (NIOX MINO, Solna, Sweden). All participants performed spirometry (Spirolab II, Rome, Italy). Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were expressed as a percentage of the predicted value (% pred.) [11]. Atopy was determined by positive skin prick test to common allergen(s) (*Dermatophagoides pteronyssinus*, *D. farinea*, Cat-Dog danders, *Alternaria alternata*, Tree mix, Grass mix, *Parietaria officinalis* pollens) (Stallergenes S.A., Antony, France). This study protocol is summarized in online suppl. 1; see www.karger.com/doi/10.1159/000513809 for all online suppl. material, and flowchart of the study protocol is illustrated in Figure 1.

Systemic Inflammatory Mediators

Peripheral blood was taken from patients and controls after 12 h of fasting and peripheral blood insulin, glucose, lipid profile, high sensitive C-reactive protein, complement 3 (C3), complement 4 (C4), and total IgE levels were assessed. HOMA-IR (Ho-

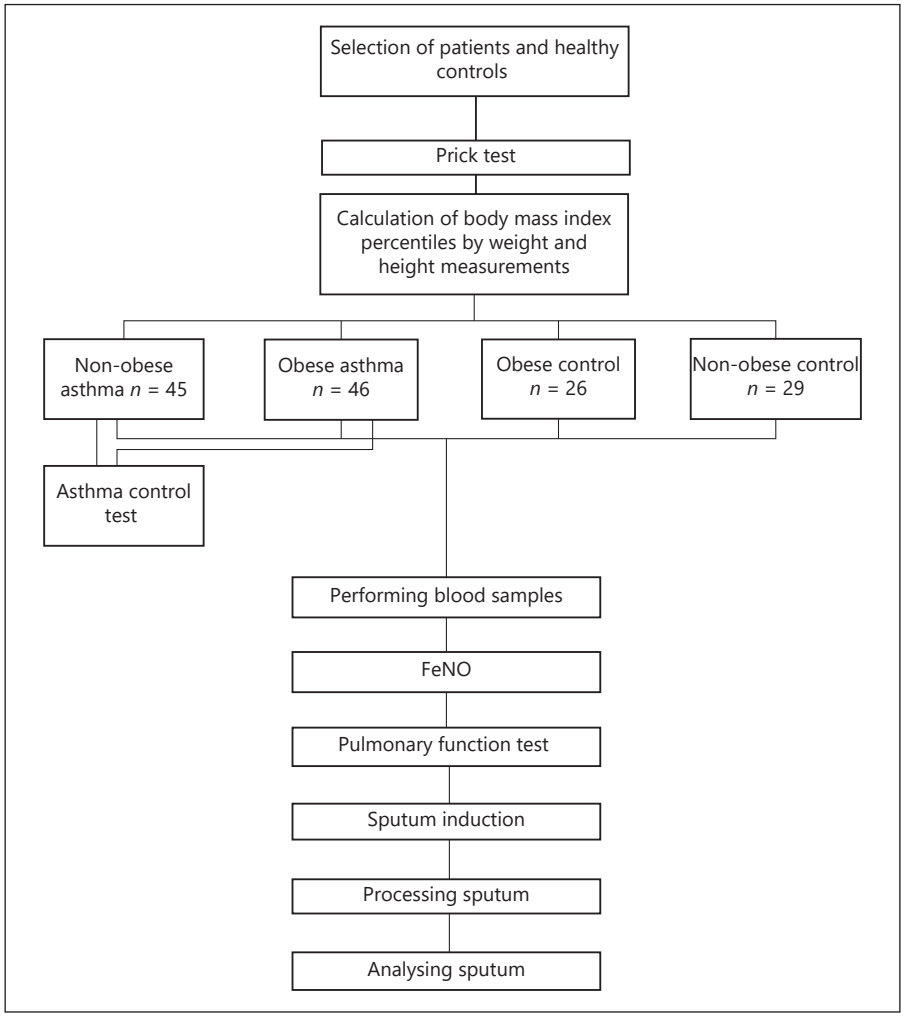

Fig. 1. Flowchart of the study protocol.

meostatic Model Assessment for Insulin) value was calculated by multiplying fasting blood glucose and fasting insulin values and dividing the result by 405 [12]. Serum total IgE levels were measured by nephelometry (Beckman Coulter Immage 800, Clare, Ireland) in all patients. Blood samples were centrifuged at 17 2,306 *g* (3,000 rpm) at 4°C for 10 min. Serum was then stored at −80°C to measure cytokine and protein levels. Serum adiponectin, chitinase (YKL-40), resistin, periostin, and leptin levels were determined by ELISA in patient and healthy control groups. The cytokine (IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-17A, TGF-β, IFN-γ, and TNF-α) levels of the participants were determined by bead-based flow cytometric assay (CBA, Becton Dickinson, Franklin Lakes, NJ, USA).

Sputum Inflammatory Cells

Participants underwent sputum induction with hypertonic saline (3%) (NEBTIME UN-600, Ultrasonic nebulizer, Japan) as previously described [13]. Sputum was selected, dispersed with dithiothreitol, and total cell counts, and viability determined. Cytospins were prepared, stained (May-Grunwald-Geimsa), and a differential cell count was obtained [14]. The method of induced sputum analysis is given in detail in online suppl. 2.

According to previous studies [15, 16], if the sputum eosinophil ratio was ≥3%, the sample was evaluated as eosinophilic sputum. Similarly, if the sputum neutrophil ratio was ≥40%, the sample was evaluated as neutrophilic sputum. If both the sputum eosinophil ratio was <3% and neutrophil sputum ratio was <40%, the sample was evaluated as paucigranulocytic sputum. If both the sputum eosinophil ratio was ≥3% and the sputum neutrophil ratio was ≥40%, the sample was evaluated as mixed cellular sputum.

Statistical Analyses

Statistical analyses were performed using the SPSS software version 20 (SPSS, Inc., Chicago, IL, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) to determine whether they were normally distributed. Descriptive analyses were presented as mean and standard deviation for normally distributed variables, median and interquartile range for non-normally distributed and ordinal variables. Categorical variables were

Table 1. Demographic and anthropometric measurements

	Patients with asthma, $n = 91$		Patients without asthma, $n = 62$		p value
	AO	ANO	NAO	NANO	
Participants, n	46	45	30	32	
Age, years	11.41±2.87	12.71±2.66	12.54±2.37	11.54±3.43	0.090[a]
Male gender, n (%)	30 (65.2)	24 (53.3)	15 (50)	15 (46.9)	0.370[b]
BMI, kg/m^2	27.37±4.49	20.72±3.35	29.62±5.12	17.99±2.81	<0.001[a]
Waist circumference, cm	91.18±12.75	75.63±11.43	96.15±14.31	67.7±8	<0.001[a]
Disease duration, months	45±35	42±37	–	–	0.709[c]
Atopy	16 (34.8)	18 (40)	–	–	0.688[b]
ICS dose	200 (0–400)	400 (0–400)	–	–	0.189[d]

ANO, asthmatic nonobese; AO, asthmatic obese; NAO, Non-AO; NANO, Nonasthmatic nonobese; ICS, inhaled corticosteroid; IQR, interquartile range. [a] One-way ANOVA test was used. Descriptive statistics were given as mean ± standard deviation. [b] Pearson χ^2 test was used. Descriptive statistics were given as n (%). [c] Independent Samples t was used. Descriptive statistics were given as mean ± standard deviation. [d] Mann-Whitney U test was used. Descriptive statistics were given as median (IQR).

summarized as numbers and percentages. Pearson χ^2 test was used in 2 × 2 tables for comparing differences between categorical variables. In comparisons of 2 independent groups, Independent Samples t test was used for normally distributed, Mann-Whitney U test was used for non-normally distributed and numerical variables. In comparisons of >2 independent groups, one-way ANOVA was used for normally distributed, Kruskal-Wallis test was used for non-normally distributed and numerical variables. The significance levels of each group were analyzed using one-way ANOVA methodology in GraphPad software for figures. Parameters without normal distribution were log transformed, while interaction statistical analysis was performed. Comparisons were made between the 4 study groups using a 2-factor ANOVA, with an obesity-by-asthma interaction. Respiratory function, sputum cell counts, and blood cytokines were the dependent variables, and obesity and asthma were the independent variables. A p value of <0.05 was considered as statistically significant.

Results

Ninety-one patients with asthma (46 obese and 45 nonobese) and 62 control patients (30 obese and 32 nonobese) were evaluated in this study. Demographic and anthropometric data and intergroup comparisons are illustrated in Table 1.

Of the asthmatic patients, 33 had mild intermittent (19 obese and 14 nonobese), 37 had mild persistent (16 obese and 21 nonobese), 12 had moderate persistent (7 obese and 5 nonobese), and 9 had severe persistent (4 obese and 5 nonobese) asthma. 63 asthmatic patients (32 obese and 31 nonobese) had well-controlled asthma and 28 had poorly controlled asthma (14 obese and 14 nonobese).

37.3% of patients with asthma had aeroallergen sensitivity. 14 patients in ANO group and 19 patients in AO group did not receive regular inhaler treatment.

Evaluation of Lung Functions

Respiratory function measurements are demonstrated in online suppl. 3. In the asthmatic groups, FEV_1 (p = 0.041), FEV_1/FVC ($p < 0.001$), and FEF2575 ($p < 0.001$) values were significantly lower compared to the nonasthmatic groups. FEV1/FVC was also significantly lower in the obese group compared to the nonobese group (p = 0.002).

FVC was significantly higher in the obese group compared to the nonobese group (p = 0.018) and obesity-asthma interaction was present (p = 0.018). FVC value was the lowest in the NANO group.

Sputum Cell Counts and FeNO

Sufficient sputum samples were obtained from 87 (56.8%) of the cases and evaluated. Table 2 shows the comparison of sputum eosinophil ratio, neutrophil ratio, and FeNO levels between groups, sputum eosinophil ($p <$ 0.01) and neutrophil ratios (p = 0.005), and FeNO (p = 0.007).

Measurements were higher in patients with asthma independent of obesity. 48 asthmatic patients (20 [43.5%] obese and 28 [62.2%] nonobese) had eosinophilic inflammation, and 11 (4 [19%] obese and 7 [25.9%] nonobese) had neutrophilic inflammation. In the asthmatic group, there were 7 patients with mixed cellular sputum inflammatory phenotype (1 [4.8%] obese and 6 [22.2%] non-

Table 2. Inflammatory cells of sputum and FeNO asthma-obesity interaction

	p value	Patients with asthma		Patients without asthma	
		AO	ANO	NAO	NANO
Patients with sufficient sputum, *n*		21	27	22	17
Sputum eosinophils (log)		1.8 (1.2–2.7)	3.7 (2.5–5.3)	0.7 (0.5–1.1)	0.8 (0.5–1.3)
O	0.058				
A	**<0.01**				
O–A	0.132				
Sputum neutrophils (log)		20.5 (14.3–29.4)	24.5 (17.8–33.4)	15.8 (11.1–22.4)	11.1 (7.5–16.6)
O	0.64				
A	**0.005**				
O–A	0.150				
FeNO (log)		20 (17.5–23)	22.64 (19.7–26)	17.46 (14.9–20)	16.44 (13.3–20)
O	0.716				
A	**0.007**				
O–A	0.26				

Sputum eosinophils, neutrophils, and FeNO levels were log transformed. Comparisons were made between the 4 study groups using a 2-factor ANOVA with an obesity-by-asthma interaction. Sputum cell counts and FeNO levels were the dependent variables, and obesity and asthma were the independent variables. *p* values are given for the main effects and the interaction: O = obese versus nonobese; A = asthma versus nonasthma; O–A = obesity-by-asthma interaction. Significant values are in bold. ANO, asthmatic nonobese; AO, asthmatic obese; NAO, Non-AO; NANO, nonasthmatic nonobese.

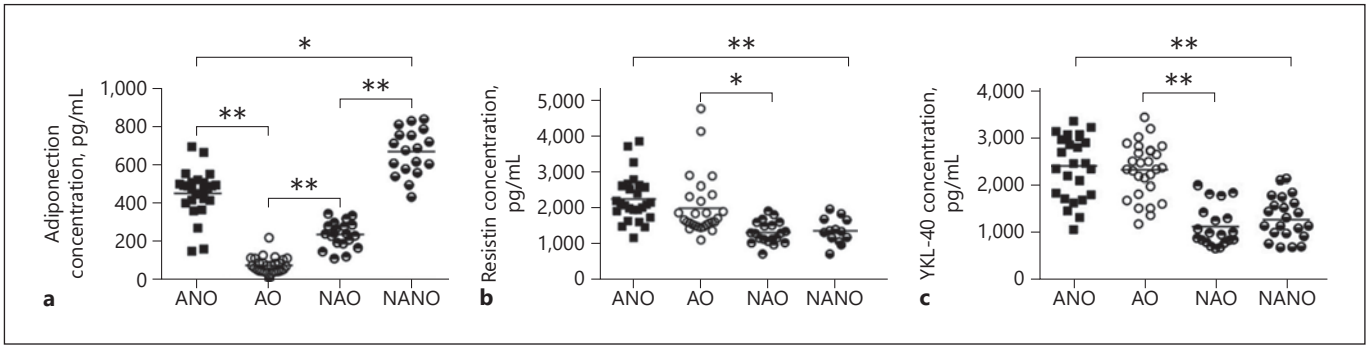

Fig. 2. Serum adiponectin levels (**a**), serum resistin levels (**b**), and serum YKL-40 levels (**c**), *$p < 0.01$, **$p < 0.001$.

obese) and 16 patients with paucigranulocytic phenotype (8 [32.8%] obese, 8 [29.6%] non-obese). YKL-40 ($p = 0.013$) and resistin ($p < 0.001$) levels were lower in those with paucigranulocytic airway inflammation (online suppl. 4).

Inflammatory Biomarkers

Table 3 demonstrates the comparison of adipokines, YKL-40, periostin levels, and leptin/adiponectin and resistin/adiponectin ratios between groups and obesity-asthma interactions. Adiponectin level was lower in asthmatics than nonasthmatics ($p < 0.001$) and obese than nonobese ones ($p < 0.001$) (Fig. 2a), and there was an interaction of obesity-asthma ($p < 0.001$). Resistin (Fig. 2b) ($p < 0.001$) and YKL-40 (Fig. 2c) ($p < 0.001$) levels were higher in asthmatics regardless of obesity. Leptin levels were higher in obese ones independent of asthma ($p < 0.001$). Intergroup comparison of serum cytokines levels and obesity-asthma interactions is given in Table 4. IL-4 (Fig. 3a) ($p < 001$), IL-5 (Fig. 3b) ($p < 0.001$), and IL-13

Table 3. Blood biomarkers and asthma-obesity interaction

	p value	Patients with asthma		Patients without asthma	
		AO, *n* = 46	ANO, *n* = 45	NAO, *n* = 30	NANO, *n* = 32
Adiponectin (log), pg/mL		64.1 (54.2–75.8)	429.2 (361.7–509.2)	225.2 (185.3–273.6)	661.1 (519.5–842.1)
O	**<0.001**				
A	**<0.001**				
O-A	**<0.001**				
Resistin (log), pg/mL		1,885 (1,687–2,106)	2,164 (1,933–2,423)	1,281 (1,126–1,458)	1,318 (1,123–1,546)
O	0.209				
A	**<0.001**				
O-A	0.404				
Periostin (log), μg/mL		34.2 (28.2–41.4)	36.9 (30.3–45.1)	33.2 (26.4–41.6)	45.9 (34.6–60.8)
O	0.083				
A	0.414				
O-A	0.285				
Leptin (log), pg/mL		3,695 (3,165–4,311)	1,122 (956–1,318)	3,543 (2,951–4,264)	1,030 (821–1,293)
O	**<0.001**				
A	0.493				
O-A	0.814				
YKL40 (log), pg/mL		1,914 (1,505–2,433)	2,377 (1,853–3,053)	1,140 (858–1,516)	1,265 (888–1,800)
O	0.266				
A	**<0.001**				
O-A	0.693				
Resistin/adiponectin (log)		29.4 (24.1–35.8)	5 (4.1–6.1)	5.6 (4.5–7.1)	1.9 (1.4–2.6)
O	**<0.001**				
A	**<0.001**				
O-A	**0.003**				
Leptin/adiponectin (log)		59.3 (47.1–74.8)	2.6 (2–3.3)	15.7 (12–20.5)	1.5 (1.1–2.1)
O	**<0.001**				
A	**<0.001**				
O-A	**0.004**				

Serum protein levels were log transformed. Comparisons were made between the 4 study groups using a 2-factor ANOVA with an obesity-by-asthma interaction. Serum protein levels were the dependent variables, and obesity and asthma were the independent variables. *p* values are given for the main effects and the interaction: O = obese versus nonobese; A = asthma versus nonasthma; O–A = obesity-by-asthma interaction. Significant values are in bold. ANO, asthmatic nonobese; AO, asthmatic obese; NAO, Non-AO; NANO, nonasthmatic nonobese

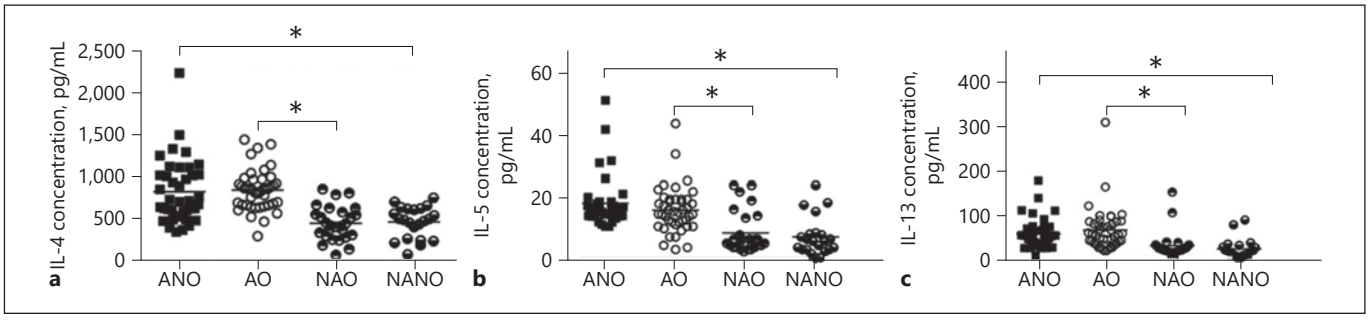

Fig. 3. Serum IL-4 levels (**a**), serum IL-5 levels (**b**), and serum IL-13 levels (**c**), *$p < 0.01$.

Table 4. Serum cytokine levels and asthma-obesity interactions

	p value	Patients with asthma		Patients without asthma	
		AO, *n* = 46	ANO, *n* = 45	NAO, *n* = 30	NANO, *n* = 32
IL-1 (log), pg/mL		3.7 (2.8–4.9)	4.7 (3.5–6.3)	5.3 (3.7–7.6)	4.3 (2.9–6.4)
O	0.945				
A	0.4				
O–A	0.191				
IL-4 (log), pg/mL		816.4 (714.7–931.6)	758.2 (661.1–870.4)	402.2 (340–475.3)	419.8 (348.6–505.2)
O	0.847				
A	**<0.001**				
O–A	0.465				
IL-5 (log), pg/mL		13.9 (11.5–16.8)	16.6 (13.7–20.2)	6.52 (5.1–8.2)	4.7 (3.6–6.1)
O	0.533				
A	**<0.001**				
O–A	**0.029**				
IL-6 (log), pg/mL		3.7 (2.2–6.4)	2.6 (1.5–4.3)	4.1 (1.9–8.6)	4.7 (2.2–10.1)
O	0.730				
A	0.304				
0–A	0.450				
IL-8 (log), pg/mL		12.4 (7.5–20.5)	125.8 (76.4–206.8)	23.1 (12.7–42.3)	14.9 (7.7–28.7)
O	**0.001**				
A	**0.009**				
O–A	**<0.001**				
IL-10 (log), pg/mL		4.3 (2.9–6.3)	4.2 (2.8–6.4)	5.8 (3.5–9.5)	9.7 (5.7–16.4)
O	0.283				
A	**0.017**				
O–A	0.253				
IL-13 (log), pg/mL		50.1 (41–61.3)	44.6 (36.2–54.9)	20.3 (15.7–26.1)	15.7 (11.6–21.2)
O	0.133				
A	**<0.001**				
O–A	0.576				
IL-17A (log), pg/mL		20.5 (13.5–31)	18 (11.8–27.4)	11.6 (7.2–18.9)	19.2 (11.1–33.3)
O	0.435				
A	0.296				
O–A	0.188				
TNF-alpha, pg/mL		214.4 (158.3–290)	208.5 (152.3–285.4)	248.8 (170.7–363.2)	283.4 (189.9–422.8)
O	0.774				
A	0.199				
O–A	0.656				
TGF-beta (log), pg/mL		79.5 (70.6–89.3)	84.6 (75–95.5)	84.7 (73.1–98.2)	63.6 (54.1–75)
O	0.115				
A	0.120				
O–A	**0.014**				
IFN-gamma (log), pg/mL		9.5 (7.6–11.9)	9.6 (7.6–12.2)	9.6 (7.2–12.8)	9.6 (7–13.2)
O	0.975				
A	0.979				
O–A	0.962				

Serum cytokine levels were log transformed. Comparisons were made between the 4 study groups using a 2-factor ANOVA with an obesity-by-asthma interaction. Serum cytokine levels were the dependent variables, and obesity and asthma were the independent variables. *p* values are given for the main effects and the interaction: O = obese versus nonobese; A = asthma versus nonasthma; O–A = obesity-by-asthma interaction. Significant values are in bold. ANO, asthmatic nonobese; AO, asthmatic obese; NAO, Non-AO; NANO, nonasthmatic nonobese.

(Fig. 3c) ($p < 0.001$) levels were higher, and IL-10 levels ($p = 0.017$) were lower in asthmatics than nonasthmatics. IL-5 level was lowest in the NANO group, and there was an interaction of obesity-asthma ($p = 0.029$).

Other Biomarkers

While there was an obesity-asthma interaction in terms of vitamin D, triglyceride, and C3 levels, no interaction was observed in terms of total IgE, eosinophil, MPV, C-reactive protein, fasting insulin, HOMA-IR, blood neutrophils, and C4 levels (online suppl. 5).

Asthma Severity and Control Level

In the asthmatic group, no significant difference was found in systemic and airway inflammation parameters in terms of asthma control (well-controlled vs. poorly controlled) and asthma severity (mild vs. moderate-severe asthma) ($p > 0.05$) (data not shown).

Discussion

In the present study, there was no interaction between obesity and asthma in terms of airway inflammation, while an interaction was demonstrated in terms of adiponectin level and resistin/adiponectin, leptin/adiponectin ratios. In the group with paucigranulocytic airway inflammation, serum YKL-40 and resistin levels were lower.

It has been indicated that adipokines (leptin, adiponectin, and resistin) secreted by adipokine tissue have receptors in the lungs. Therefore, it is believed that these mediators can be effective in the obesity-asthma relationship. Adiponectin is an anti-inflammatory adipokine secreted only from adipocytes [17], and hypoxia, pro-inflammatory cytokines, and oxidative stress reduce the level of adiponectin [18]. Adiponectin levels decrease with increased obesity and inflammatory response [5, 19]. Adiponectin is thought to induce anti-inflammatory activities through decreased TNF-α production, increased production of anti-inflammatory cytokine IL-10, and induction of receptor antagonists for IL-1 and IL-6 [5]. In a review of studies on adiponectin, it was emphasized that adiponectin played an important role at the systemic level, and hypoadiponectinemia was associated with many diseases such as atherosclerotic cardiovascular diseases and cancer [20]. Adiponectin deficiency increases allergic inflammation and pulmonary vascular remodeling in the chronic asthma model [21]. Mouse experiments have shown that adiponectin reduces allergen-induced airway inflammation and hypersensitivity [22]. Furthermore, it has been indicated that exogenous adiponectin promotes the proliferation of human bronchial epithelial cells, cell cycle, and wound repair [23]. In the present study, lowest adiponectin levels were determined in the obese-asthma group, and obesity-asthma interactions were detected. Low adiponectin in the obese group compared to the nonobese group has been shown in previous studies [24]. In the present study, however, it was found that adiponectin was lower in the AO group than the NAO group (64.1 vs. 225.2) and lower in the ANO group than the NANO group (429.2 vs. 661.1). Adiponectin was also lower in asthmatic patients than in controls. Based on these results, it can be said that asthma on its own also leads to reduced adiponectin levels. This may be due to increased oxidative load in asthma [25, 26]. Increased oxidative stress in asthma can reduce adiponectin levels, causing increased remodeling and a decrease in anti-inflammatory response. Zhu et al. [27] have shown that exogenous adiponectin in obesity-associated asthmatic mice alleviates oxidative stress and exacerbation of airway inflammation. Based on this information, it can be argued that adiponectin may be indicative of obese-asthma phenotype in children, and adiponectin can be considered as a treatment option for this phenotype. There is a need for extensive studies on larger populations.

Resistin is produced mainly by adipocytes in rodents, and its effects on obesity and insulin resistance are known. In humans, unlike rodents, it is produced mainly by mononuclear cells of peripheral blood, and the results regarding its role in obesity and insulin resistance are contradictory [28]. Many human studies failed to demonstrate a correlation between serum resistin levels and BMI, whereas a correlation between body fat ratio was detected [29, 30]. In contrast, there are also studies showing no correlation with parameters indicating body fat ratio [31]. Despite the fact that the role of resistin in obesity and insulin resistance is not comprehensively known in humans, it is known to have a definite role in pro-inflammatory processes, which are absolutely associated with the development of obesity and insulin resistance [32]. Circulating resistin can be a central messenger between inflammation and insulin homeostasis [33, 34]. Resistin has a pro-inflammatory effect on peripheral blood mononuclear cells and vascular cell types through various signaling mechanisms [28]. Resist is also shown to play a role in airway remodeling [35] and increase the expression of mucin gene in airway epithelial cells [36]. Various clinical trials have reported higher resistin levels in asthmatic cases than controls. In the present study,

similar to the previous study of Ballantyne et al. [37], resistin levels did not show any difference between obese and nonobese groups, but resistin levels in asthmatic cases were significantly higher compared to nonasthmatic cases. In addition, highest resistin/adiponectin ratio was detected in the obese-asthma group and obesity-asthma interaction was observed. Based on these results, it can be proposed that resistin/adiponectin ratio is a better indicator for obese-asthma phenotype in children. Further studies on this topic are needed.

Chitinases are evolutionarily preserved proteins that mediate airway inflammation in asthmatic mice models [38]. The chitinase-like protein YKL-40 is devoid of chitinase activity, but it binds chitin expressed in all tissues and leads to the development of inflammation and tissue remodeling [39]. Previous studies have found that the level of YKL-40 was higher in patients with asthma, but its correlation with asthma severity was found to be contradictory [40–42]. In the present study, serum YKL-40 levels were higher in children with asthma than healthy controls, independent of obesity. In addition, there was no correlation between serum YKL-40 levels and asthma control level and severity. Serum YKL-40 levels in adults have been found to be generally associated with asthma severity, phenotype, and control status [43–47]. YKL-40 levels are higher in asthmatic children than healthy cases; however, consistent with the present study, no relationship has been found between asthma severity and control levels [41, 48]. Similar to our results, Santos et al. were unable to demonstrate a relationship between serum YKL-40 levels and asthma severity in children [41]. Spectalzki et al. showed that serum YKL-40 levels were higher in adult obese-asthma cases compared to adult nonobese asthma cases. Different results obtained in the present study and the study of Spectalzki et al. [42] may be due to the different sample groups. In the present study, YKL-40 and resistin levels were lower in patients with paucigranulocytic inflammation, which were considered to have less severe airway inflammation. However, there was no correlation with the severity of asthma. A study in adults showed that resistin levels may be a marker of disease severity in patients with asthma, and YKL-40 is correlated with asthma phenotype in adults [41, 45]. In the literature, there is no study investigating the relationship between resistin levels and the severity of asthma in children. It is known that there may be differences in the pathophysiological characteristics of adult and child asthma. This may be one of the reasons why YKL-40 shows a difference between adults and children. Further studies are needed on this topic.

Asthma due to obesity can be accompanied by high or low airway inflammation, which is evaluated by FeNO, depending on the speed of the increase in lipoidosis. Rapid lipoidosis can increase the risk of childhood asthma and airway inflammation [49]. There are studies showing that sputum eosinophil ratio in adults is correlated with FeNO. In the present study, there was a positive correlation between FeNO and sputum eosinophil levels in the asthma group. In adult studies, it has been shown that in the obese-asthma phenotype, sputum inflammatory cells tend to be more neutrophilic in general. Obesity has been shown to be associated with nonatopic inflammation by dysregulated DNA methylation in children [50]. To the best of our knowledge, there is only one study examining inflammatory cells in the sputum for airway inflammation in obese-asthmatic children [51]. In this study, no difference was detected in obese asthma in terms of airway and systemic inflammation in children. In the present study, sputum eosinophil ratio was higher in patients with asthma than in controls. Although not statistically different, sputum eosinophil ratio was lower, and sputum neutrophil ratio was higher in obese-asthmatic children than nonobese asthmatic children. In addition, FeNO levels were higher regardless of obesity in patients with asthma, but there was no difference in obese asthma compared to nonobese asthma, and obesity-asthma interaction was not detected. Furthermore, rates of lipoidosis of the patients in the present study were not known. This may be the reason why obese-asthma airway inflammation pattern did not differ in the present study.

Present study is the first study that investigates airway and systemic inflammation in children with obese asthma in a multifaceted manner. Due to the lack of previous data to estimate sample size, 2 control groups were included in the study, resulting in a more thorough assessment of obesity-asthma interactions. In addition, patients who had not undergone systemic steroid therapy or did not have infection in the last 4 weeks were carefully selected, even though we could not interrupt inhaled steroid therapy. Patients with atopy were excluded from nonasthmatic groups.

In conclusion, the relationship between obesity and asthma in children was investigated in a multifaceted manner in the present study, and no interaction was found between obesity and asthma in terms of airway inflammation. Interaction between obesity and asthma was shown in terms of adiponectin level and resistin/adiponectin and leptin/adiponectin ratios. It was found that serum YKL-40 and resistin levels could be associated with airway inflammation.

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Statement of Ethics

All participants provided written informed consent. This study was approved by the Ankara Children's Hematology Oncology Training and Research Hospital Institutional Review Boards (2015; No. 020).

Conflict of Interest Statement

On behalf of all authors, the corresponding author states that there are no conflicts of interest to declare.

Author Contributions

E.V., E.C., and C.N.K. conceived and designed the study. E.V. was involved in analyses and interpretation of data and drafting manuscript. E.D.M., M.T., M.Ç., M.Ö., and F.D. performed data collection. E.K. was evaluated sputum cell counts. E.C., T.K., İ.G., and C.N.K. were involved in manuscript revision and performed overall supervision.

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