

The Association between Asthma and Obesity in Children – Inflammatory and Mechanical Factors

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Abstract

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BACKGROUND: Association of asthma and obesity has been demonstrated in numerous epidemiological studies. However, the underlying mechanisms of the association are not well understood. Both conditions are characterised by chronic tissue inflammation, which includes numerous different inflammatory markers, and possible atopy.

AIM: The study aimed to investigate the association between asthma and obesity in children and assess several of potential underlying mechanisms, including the parameters of systemic inflammation (CRP, fibrinogen) and the mechanical effect of obesity on the respiratory system through parameters of lung function. An additional aim was to examine the role of atopy in overweight children with asthma and to investigate the type of respiratory inflammation.

MATERIAL AND METHODS: This prospective study included 72 patients in the age group of 7-15 years, including 38 with high body mass index (BMI), 16 with asthma and normal BMI, and 18 with asthma and high BMI for sex and age. Non-specific inflammatory markers (fibrinogen, CRP), eosinophilia, and total serum IgE were investigated. The patients underwent a skin prick test (SPT) with standard inhalant allergen extracts, measurement of fractional exhaled nitric oxide Fe (NO), and an assessment of lung function.

RESULTS: In overweight groups of children we determined significantly higher values ($p < 0.001$) of both acute inflammatory reactants, CRP and fibrinogen, with no difference between children with and without asthma. There was a significant increase in eosinophilia, total IgE, and positive SPT in the asthmatic groups compared to the group of non-asthmatic patients ($p < 0.001$ for the three parameters). Compared to the group composed of overweight patients without asthma, the asthmatic patients had higher NO values ($p < 0.001$). No significant difference in the lung function parameters was found between the three groups ($p > 0.05$).

CONCLUSION: A positive association between asthma and obesity with inflammation as an underlying mechanism, eosinophilic one in asthmatic patients and non-eosinophilic one in overweight patients, was determined. It seems that the lung function parameters did not differ between asthmatic patients and overweight patients. No influence of atopy in the association between asthma and obesity was verified. Further analyses of specific inflammatory markers, for an in-depth evaluation of the mechanisms leading to the association of obesity and asthma, are warranted.

Introduction

Recently, a parallel epidemic increase in the prevalence of asthma and obesity in children has been observed. With more than 334 million patients worldwide, asthma is considered one of the most common chronic diseases. The International Study of

Asthma and Allergies in Childhood (ISAAC) has found a wide variation in the prevalence of asthma in childhood [1]. Within this study, in the period between 2002-2004, a moderate low prevalence of asthma has been reported in the Republic of Macedonia that was due, at least partially, to under-diagnosis [2]. The increasing trend in the prevalence of asthma in both adults and children in the last decade has reached a

plateau in developed countries. However, the rise of obesity prevalence has been established recently in developing countries, including Macedonia [3]. Worldwide obesity has been nearly tripled since 1975 as a consequence of changes in diet and the decrease in overall physical activity. Obesity has become a major public health problem, especially in developed countries with more than 1.9 billion overweight people, 600 million of which were obese [4]. Within ISAAC, a moderately low prevalence of overweight children and the low prevalence of obese children have been reported in the Republic of Macedonia [5]. However, thirteen years later, in a new epidemiological study, a significant increasing trend in the prevalence of overweight/obese children has been identified [6].

The relationship between asthma and obesity has been demonstrated in numerous epidemiological studies, but underlying mechanisms of this association are not well understood. Obesity increases the prevalence of asthma and asthma-like symptoms, compromises the control of the disease, decreases the response to anti-inflammatory therapy, and impairs the quality of life in patients with asthma. The physical or mechanical effect of the adipose tissue on the respiratory system is manifested by a reduction in pulmonary volumes and respiratory compliance [7]. On the other hand, the mechanical effect of obesity upon the respiratory system can affect the contractile power of the smooth muscle of the bronchial trunk inducing bronchial hyperreactivity [8]. Both conditions are characterised by chronic tissue inflammation, which includes numerous, although different inflammatory markers which may increase the bronchial hyperreactivity in patients with asthma [9]. Obesity promotes a low-grade chronic inflammatory state. Both, cellular and humoral immunity are reprogrammed to function under excessive body weight [10]. The number of leucocytes and lymphocytes correlates with the degree of obesity, as well as with the monocyte/macrophage ratio. They secrete a large number of inflammatory cytokines such as tumour necrotic factor-alpha (TNF- α), interleukin-6 (IL-6), plasminogen activator (PAI-1), macrophage chemotactic protein (MCP-1).

Moreover, an increase in the level of acute-phase inflammatory reactants such as C-reactive protein (CRP), fibrinogen, and complement components, especially in abdominal obesity can be observed [11], [12]. On the other hand, mediators contribute to increased IgE production, subepithelial fibrosis, and remodelling of the bronchial trunk, which is the primary observation in the pathogenesis of asthma [13]. Adipocytes also produce numerous hormones, such as leptin and adiponectin, which can affect the respiratory system directly, because of the expression of leptin receptors in the lung [14] or through the cells of the immune system [15]. Atopy is an important factor in the development of childhood asthma, present in over 80% of children with asthma.

Most of the studies, however, suggest that inflammation of the airway in obese asthmatic adults is non-eosinophilic, with significant neutrophilia in the induced sputum [16].

In this study we sought to investigate the association between asthma and obesity in children and to establish some of the potential underlying mechanisms with particular emphasis on the parameters of systemic inflammation (CRP, fibrinogen) and the mechanical effect of adipose tissue upon the respiratory system through the parameters of the lung function as well as to explore the role of atopy in overweight children with asthma and the type of respiratory inflammation.

Material and Methods

The study has been approved by The Ethics Committee at the Medical Faculty in Skopje. Written informed consent for inclusion in the study was obtained by the parents. The study was a prospective cross-sectional and included 72 children aged 7-15 years (11.08 ± 2.23), treated as outpatients or inpatients at the University Children's Clinic, Skopje, from March to October 2018. Patients were divided into three groups: Group 1 consisted of 38 children with a high body mass index (BMI); Group 2 consisted of 16 children with asthma and a normal BMI; Group 3 consisted of 18 patients with asthma and high BMI. Exclusion criteria included other respiratory, gastrointestinal, urogenital, and cardiovascular diseases, as well as obesity-associated with other than asthma disease or syndrome, and administration of systemic corticosteroid therapy three months before being included in the study. Medical history was taken from the parents and included questions about the familial history of diabetes mellitus and atopy, premature birth, breastfeeding in the first year of life and passive exposure to cigarette smoke at home. Each patient underwent through clinical check-up including auxology measurements. The following laboratory analyses were performed in each child: blood counts for eosinophils, systemic inflammatory markers (fibrinogen, CRP), and total serum IgE.

BMI was calculated by a standard formula and expressed as a weight (kg)/height(m)². The International cut-off points for BMI for overweight and obesity by sex between 2 and 18 years, defined to pass through a BMI of 25 kg/m² for overweight and 30 kg/m² for obesity at age 18, were used [17]. For abdominal obesity assessment, the waist circumference (WC) was measured in centimetres between the lower border of the ribcage and midline of the iliac crest, as well as the hip circumference (HC) in centimetres from the widest point of the hips, and then the waist-hip ratio (WHR) was calculated as previously described [18]. Reference values were

used by sex and age, defined above the 90th percentile for abdominal obesity [19].

Skin prick test (SP) was performed using commercial inhalant allergen extracts, i.e. a mixture of grass pollen, a mixture of trees pollen, Dermatophagoides pteronyssinus, Dermatophagoides farinae, cat epithelium, dog epithelium, mould, and cockroach. The test was performed at the volar side of the forearm where drops of commercial allergen extract Allergopharma (Reinbek, Germany) were gently pricked on the skin surface with a separate lancet. The distance between drops was not less than 2 cm. One mg/ml of histamine or saline were used as positive or negative control solutions. The test was interpreted 15 minutes after the administration of allergen extracts, in comparison with the histamine and the saline reaction. Atopy was defined as a positive response to 1 or more inhalant allergens [20].

The assessment of pulmonary function was performed with the spirometer Schiller SP-1 [21], [22]. Spirometric parameters FEV1, FVC, FEV1/FVC ratio or Tiffeneau index, peak expiratory flow (PEF), and forced expiratory flows in 25%, 50%, 75% of FVC (FEF25, FEF50, FEF75) were assessed. The results were expressed in per cent of predictive value for gender and age [23]. Spirometric measurements were repeated 15 minutes after administration of 200 mcg of salbutamol (albuterol) through a metered-dose inhaler and a Volumatic spacer device. An increase in FEV1 of 12% over baseline was considered as a significant bronchodilator response.

The assessment of eosinophilic airway inflammation was carried out by measuring fractional exhaled nitric oxide-Fe (NO) using NO analyser Niox Vero (Uppsala, Sweden). After maximum inspiration, the patients exhaled air without prior retention at a speed of 50 m/s. Values < 20 ppb in childhood indicated non-eosinophilic airway inflammation, or a stable clinical condition [24].

Statistical Analyses

Data was statistically analysed in SPSS software package, version 22.0 for Windows (SPSS, Chicago, IL, USA). The qualitative series were processed by determining the coefficient of relations, proportions, and rates, and were shown as absolute and relative numbers. Quantitative series were analysed with measures of central tendency (average, median), as well as with dispersion measures (standard deviation, standard error).

The distribution of frequencies was analysed through the Shapiro-Wilk test. Pearson Chi-square test, Yates corrected, Fischer exact test, and Fisher Freeman Halton exact test was used to determine the association between certain attributive dichotomies. To test the significance of the difference between certain analysed numerical parameters, depending on the frequency distribution, Student's t-test, One Way

ANOVA test, Mann Whitney U test and the Kruskal-Wallis H test were conducted. A two-sided analysis with a significance level of $p < 0.05$ was used to determine the statistical significance.

Results

The survey included a total of 72 children. According to the clinical diagnosis, 38 (52.8%) were overweight/obese without asthma, 16 (22.2%) were asthmatic with normal BMI, and 18 children (25%) were overweight/obese suffering from asthma. The average age of the children in the three groups was 11.4 ± 2.1 , 11.0 ± 2.4 and 10.9 ± 2.1 years, respectively without a significant difference between the groups ($p = 0.835$).

Children with asthma in both groups, in the group with normal BMI and high BMI, had a significantly higher frequency of familial atopy compared to the group with high BMI without asthma ($p = 0.034$). There was no significant association between the groups regarding sex ($p = 0.859$), the familial history of diabetes mellitus ($p = 0.139$), premature birth ($p = 0.111$), breastfeeding in the first year of life ($p = 0.769$) and passive exposure to cigarette smoke at home ($p = 0.265$), (Table 1).

Table 1: Demographic characteristics of the patients

Parameters	Groups of children according to the clinical diagnosis			P
	Overweight/obesity N = 38	Asthma N = 16	Overweight/obesity and asthma N = 18	
Sex (male)	27 (71.05%)	12 (75%)	14 (77.78%)	** $p = 0.859$
Age	11.37 ± 2.19	11.00 ± 2.42	10.89 ± 2.09	*** χ^2 (2) = 0.359; $p = 0.835$
Fam. atopy	19 (50%)	13 (81.25%)	14 (77.78%)	** $p = 0.0338^*$
Fam. history of diabetes	15 (39.47%)	2 (12.50%)	5 (27.78%)	** $p = 0.139$
Premature birth	9 (23.68%)	1 (6.25%)	1 (5.56%)	** $p = 0.111$
Smokers at home	27 (71.05%)	9 (56.25%)	9 (50%)	† 2.652; $df = 2$; $p = 0.265$
Breastfeeding period	4 (10.53%)	2 (12.5%)	1 (5.56%)	** $p = 0.769$
non breastfed	2 (5.25%)	0 (0%)	0 (%)	
> 1 ≤ 4 months	10 (26.32%)	2 (12.5%)	3 (16.67%)	
> 4 ≤ 6 months	22 (57.89%)	12 (75%)	14 (77.78%)	
> 6 ≤ 12 months				

* $p < 0.05$; ** Fisher Freeman Halton exact test; *** Kruskal-Wallis H test; † Pearson Chi-square.

There was a significant difference between the patients from the three groups regarding the average value of the following non-specific inflammatory markers: a) eosinophilia-elevated values above normal (> 4%) were detected in children with asthma both with normal and with high BMI compared to the overweight children without asthma ($p = 0.001$); b) CRP values were higher in the overweight groups ($p = 0.004$); c) fibrinogen levels were higher in the overweight groups ($p = 0.001$); d) IgE levels were higher in the patients with asthma ($p = 0.001$), (Table 2).

Table 2: Analysis of non-specific inflammatory markers and other parameters analysed according to the clinical diagnosis

Parameters	Groups of children Overweight/obesity n = 38	Asthma n = 16	Overweight/obesity and asthma n = 18	P
WBC	8.52 ± 2.32	7.31 ± 1.98	8.25 ± 2.02	** $\chi^2(2) = 3.955$; p = 0.138
Eo	2.60 ± 2.35	6.46 ± 4.77	5.75 ± 2.79	** $\chi^2(2) = 17.992$; p < 0.001*
CRP	3.92 ± 3.54	1.47 ± 2.56	3.93 ± 6.31	** $\chi^2(2) = 11.304$; p = 0.004*
Fibrinogen	3.04 ± 0.46	2.52 ± 0.40	2.78 ± 0.41	*** F = 8.357; p = 0.001*
IgE	119.75 ± 189.11	374.02 ± 494.97	380.17 ± 333.39	** $\chi^2(2) = 19.566$; p < 0.001*
FEV1	103.79 ± 10.59	97.21 ± 10.74	102.21 ± 12.36	** $\chi^2(2) = 3.221$; p = 0.120
FVC	98.74 ± 9.89	95.99 ± 8.59	99.52 ± 8.47	*** F = 0.6735; p = 0.513
FEV1/FVC	99.01 ± 7.89	95.90 ± 8.92	96.47 ± 6.73	** $\chi^2(2) = 3.191$; p = 0.203
PEF	85.24 ± 11.79	87.82 ± 27.28	82.18 ± 14.18	** $\chi^2(2) = 2.942$; p = 0.230
FEF25	81.26 ± 22.41	71.04 ± 27.06	73.69 ± 21.38	*** F = 1.298; p = 0.280
FEV50	49.13 ± 13.99	55.76 ± 15.73	49.31 ± 17.02	*** F = 1.163; p = 0.319
FEV75	94.72 ± 17.14	81.74 ± 21.64	87.18 ± 17.73	** $\chi^2(2) = 8.172$; p = 0.017*
FeNO (>20 ppb)	15.59 ± 9.93	43.83 ± 29.27	39.07 ± 25.01	** $\chi^2(2) = 16.738$; p < 0.001*
BMI	30.38 ± 5.57	18.59 ± 2.01	28.83 ± 5.24	*** F = 33.249; p < 0.001*
WC	95.75 ± 19.69	39.06 ± 31.39	90.61 ± 11.09	** $\chi^2(2) = 36.427$; p < 0.001*
WHR	0.94 ± 0.10	0.86 ± 0.07	0.94 ± 0.12	** $\chi^2(2) = 4.278$; p = 0.118
SPT (positive)	4 (10.53%)	13 (81.25%)	16 (88.89%)	Yates correcting = 41.768; df = 4; p = 0.000001**
Bronchodilator test (positive)	7 (18.92%)	14 (87.50%)	16 (100%)	/

FeNO = fractional exhaled nitric oxide; BMI = body mass index; WC = waist circumference; WHR = waist-hip ratio; * p < 0.05; ** Kruskal-Wallis H test; *** One Way ANOVA test.

Regarding the spirometric parameters, there was a significance only about FEV75, which was the lowest in the asthma group (p = 0.017). Regarding all other parameters, there was no significant difference between the three examined groups. High FeNO values had the children from the asthma groups (p = 0.001). There was a significant association between the parameter of personal atopy-SPT and asthma diagnosis (p = 0.001). Positive bronchodilator test was detected in 14 children with asthma (87.50%), in 18 children (100%) in an overweight/obese group with asthma, and 7 children (18.92%) in the group with high BMI.

Discussion

The positive association between asthma and obesity has been reported in many studies. Recently, a meta-analysis related to the BMI and asthma association has been published, which has confirmed that being overweight or obese increase the risk of asthma by 1.64 and 1.92, respectively [25]. Most of the studies included in this meta-analysis have supported a female-specific association. However, others have suggested no gender difference [12]. In our study, there was no significant difference regarding gender distribution between the groups.

Children with high BMI have been found to have elevated values of the acute-phase inflammation reactants, CRP and fibrinogen, not depending on asthma. Most studies have reported an elevated CRP level in obese children and adults [15], [16]. Visser et al., have pointed out that CRP increases with BMI. Regarding the level of fibrinogen, published studies are inconsistent [26]. Canöz and Hafez have determined an elevated level of fibrinogen in overweight subjects, especially in the presence of abdominal obesity [16], [27]. Buyukozturk has not established a correlation between obesity, asthma, and fibrinogen level [28]. In our study, there was no difference between asthmatic children with normal or high BMI regarding eosinophilia, total IgE antibodies, and positive SPT. For these markers, significantly higher values were found in asthma groups compared to the overweight/obese group.

Additionally, asthma groups had significantly higher FeNO values and greater occurrence of familial atopy, which all support the eosinophilic allergic basis of asthma, most common in childhood. FeNO is considered as a marker of eosinophilic airway inflammation. Thus it is high in atopic asthma. On the other hand, asthma in obese adults is usually non-allergic, with neutrophilia in induced sputum [20]. The results of this study support the positive association between asthma and obesity with inflammation as a common underlying mechanism, eosinophilic one in asthma and non-eosinophilic one in obesity. Atopy was not established as an underlying mechanism. Contrary to our results, Rastogi has not established systemic and airway inflammation in overweight children with asthma, investigating FeNO, eosinophils in induced sputum, CRP, and IL-6 [29].

In addition to BMI in the assessment of overweight and obesity, some authors like Appleton and Kronander have included other parameters, such as WC, which better correlates with abdominal obesity in children with asthma [30], [31]. Bustos et al., have confirmed the association between asthma and BMI, but not regarding WC. We assessed the nutritional status by examining BMI, WC, and WHR in the three study groups and found a positive association of the overweight/obese groups either with BMI or with WC. Abdominal fat and visceral fatty tissue are considered the main source of inflammatory markers that makes obesity a "pro-inflammatory condition" [32].

Given the goal of our study to examine the mechanical effect of obesity on lung function, the children with asthma were stable with normal lung function, i.e. not in the stage of exacerbation when the functional parameters would have been reduced. Additionally, all patients with asthma received anti-inflammatory therapy with inhaled corticosteroids. Although the values of the investigated pulmonary functional parameters were within the limits of the reference among all three groups of children, we did not find a significant difference in the mean values between them. Only a significantly lower FEV75 value

was found in the group of children with asthma, which is a parameter for estimating the airflow in the small airways. This is understandable because asthma is a chronic inflammatory disease predominantly affecting small airways. In obesity, due to increased intra-abdominal pressure by adipose tissue on the diaphragm, a pressure on lung and chest is also increased, reducing its elasticity and thus leading to a decrease in residual volume (RV) and forced respiratory capacity (FRC). A large longitudinal study involving children and adults with asthma has reported a significant reduction in FVC in obese adults but not in children [33]. In children with BMI above 85th percentile, a significant reduction in FEV1/FVC ratio has been demonstrated [34]. However, there are some published studies in overweight children with asthma that have reported normal static volumes, but poor control of asthma due to the impaired perception of dyspnoea, which also occurs because of reduced elasticity of the chest [35], [36]. The absence of a significant difference in pulmonary function parameters between asthmatic children and overweight children might be in favour of the influence of mechanical factors in their association.

Bronchial hyperreactivity (BHR), a major feature of asthma, was tested with a bronchodilator test which was positive in over 87% of the asthma groups, but also 26% of the overweight children. There are studies suggesting BHR in obese adults, although they do not include children. Due to obesity, the lumen of the airway is reduced, which leads to disturbed function of the smooth muscle and over time leads to bronchospasm and BHR [37]. Another study has suggested that there was no difference in BHR, by bronchoprovocation test, between asthmatic overweight children and children with normal BMI [38]. Van Leeuwen et al. have confirmed that after weight reduction in children with asthma, the severity of exercise-induced airflow obstruction decreased and the quality of life improved [39].

The present study has some limitations. The number of children in the three examined groups was not similar in the time of the analyses, where the group composed of overweight patients was larger than the other two groups. Additionally, to avoid bias because of the small sample, obese patients were included in the overweight group.

A positive association between asthma and obesity with inflammation as an underlying mechanism was identified, eosinophilic inflammation in asthmatic patients and non-eosinophilic inflammation in overweight patients. It appears that the parameters of lung function did not differ in asthma and obesity. The role of atopy in the association between asthma and obesity was not established. Further investigations are required, including specific inflammatory markers for a more detailed clarification of the underlying mechanisms.

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