

The Effect of Obesity on the Level of Fractional Exhaled Nitric Oxide in Children with Asthma

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Key Words

Airway inflammation · Asthma · Body mass index · Exhaled nitric oxide · Insulin resistance · Metabolic syndrome · Obesity

Abstract

Background: Several studies have demonstrated a relationship between asthma and obesity. However, the results have been conflicting with regard to the relationship between fractional exhaled nitric oxide (FeNO), used as a marker of airway inflammation in asthmatic patients, and obesity. We aimed to evaluate the association of FeNO with obesity and obesity-related metabolic complications in asthmatic and nonasthmatic children. **Methods:** The study population included children aged between 6 and 17 years and consisted of 4 groups: obese asthmatics (n = 52), normal-weight asthmatics (n = 49), obese nonasthmatics (n = 51) and normal-weight nonasthmatics (n = 42). FeNO measurement and spirometry were performed for all patients. To evaluate the metabolic complications, serum lipids, glucose and insulin levels were measured. Insulin resistance (IR) was estimated by the homeostasis model assessment, HOMA-IR. All participants were evaluated for the presence of metabolic syndrome (MS). **Results:** The mean age for the 194 subjects par-

ticipating in the study was 11.6 ± 2.5 years. The FeNO level of asthma patients with MS was not different from those without MS (14.5 ± 8.0 and 16.7 ± 8.7 , respectively, $p = 0.449$). In the nonasthmatic group, subjects with MS had a higher FeNO level than subjects without MS (12.5 ± 5.1 and 17.3 ± 8.3 , respectively, $p = 0.014$). Spearman's rank correlation coefficients revealed a positive correlation between FeNO and body mass index (BMI; $p = 0.049$, $r^2: 0.204$) in the nonasthmatic group and after multivariate regression analysis, BMI still persisted as an independent risk factor for FeNO. **Conclusion:** We found a positive correlation between BMI and FeNO level which suggests a link between obesity and increased airway inflammation in nonasthmatic children.

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Introduction

Asthma and obesity affect millions of people; each is a significant public health problem. The simultaneous rise in the prevalence of both obesity and asthma and their frequent coexistence in the same patient suggest that obesity is more prevalent among asthmatic children and is related to the severity of the respiratory symptoms [1–4]. Studies have also shown that asthma is more prevalent in

overweight patients and that body mass index (BMI) is positively associated with asthma severity [5, 6].

These studies indicate that the relative risk of asthma increases with BMI and that obesity appears to be associated with asthma severity, but the underlying mechanisms have not been completely explained. It has been established that obesity can impose a mechanical load on the diaphragm and decrease expiratory residual volume and functional residual capacity [7]. Besides the mechanical effect of obesity on lung functions, recent studies have shown that the inflammatory burden associated with obesity may contribute to increased airway inflammation [8–10].

Fractional exhaled nitric oxide (FeNO) is being used as a marker of airway inflammation in asthmatic patients. There have been conflicting results on the relation between exhaled nitric oxide levels and obesity and body composition. While some studies have not shown a link between FeNO and obesity [11, 12], in other studies obesity has been associated with higher [13, 14] as well as lower FeNO levels [15] a recent study found no link between FeNO and obesity [16].

Given the conflicting results from the previous studies, we aimed to investigate the association of FeNO with obesity and obesity-related metabolic complications in asthmatic and nonasthmatic children.

Methods

Study Design and Participants

This cross-sectional study was undertaken between November 2010 and March 2011. The study population consisted of 4 age- and sex-matched groups including children aged between 6 and 17 years: obese asthmatics, normal-weight asthmatics, obese nonasthmatics and normal-weight nonasthmatics. The groups were recruited consecutively from the admissions to the outpatient clinics of the Departments of Pediatric Allergy, Pediatric Endocrinology and Pediatrics.

Definitions

Asthma. Asthma was defined as typical symptoms including paroxysmal wheezing, breathlessness, chest tightness or coughing with either an increase in FEV₁ of at least 12% after bronchodilator therapy or significant airway hyperresponsiveness [17].

Asthma control: The control status of asthma was determined by the pediatric allergist according to GINA criteria including the frequency of the present symptoms, nocturnal symptoms, the use of rescue bronchodilators, the degree of limitation in daily activities and lung function [17].

Obesity. Obesity was defined as a BMI >95th percentile for age and sex. Height and weight were measured by trained technicians using standardized protocols and calibrated equipment.

Metabolic Syndrome. All study participants were evaluated for MS. It was defined using previously described data adapted from

World Health Organization (WHO) guidelines [18]. According to these guidelines, hyperinsulinism and/or impaired glucose tolerance were essential plus any two of the following three criteria: (1) BMI ≥95th percentile for age and sex, (2) systolic blood pressure ≥95th percentile for age, sex and height and (3) triglyceride ≥105 mg/dl for children under 10 years of age and ≥136 mg/dl for children older than 10 years of age and/or high-density lipoprotein <35 mg/dl.

Inclusion and Exclusion Criteria

According to GINA, asthmatic patients had had asthma for at least 1 year prior to study enrollment and controlled asthma at the time of the study. Patients whose asthma was not considered as being controlled during the study were not included. Healthy subjects without any history of underlying lung disease or allergic rhinitis were recruited for the nonasthmatic groups.

Children who were actively smoking or with a disease that could interfere with the study results, e.g. heart disease, diabetes or chronic inflammatory diseases like juvenile rheumatoid arthritis, were also not included.

The study was approved by the local ethics committee and written consent was obtained from all children and their parents.

Laboratory Investigations

FeNO. FeNO was performed with a portable airway inflammation monitor (NIOX MINO, Solna, Sweden) with a constant flow of 50 ml/s, according to European Respiratory Society/American Thoracic Society criteria [19], and was expressed as parts per billion (ppb). The children were instructed to avoid strenuous exercise, eating and drinking for 2 h before FeNO measurements.

Spirometry. Lung function tests were performed with a spirometer (Spirolab II, Rome, Italy) to meet American Thoracic Society standards [20]. Study members were seated in the upright position; at least 3 acceptable maneuvers were obtained and the best FEV₁ was used. Testing equipment was calibrated daily to ensure accuracy and precision.

Skin Prick Test. Epidermal prick tests was performed on all patients with common airborne allergens including house-dust mites (*Dermatophagoides pteronyssinus* and *D. farinea*), cat and dog danders, *Alternaria alternata*, mixed tree, mixed grasses and *Parietaria officinalis* pollens (Stallergenes S.A., Antony, France) together with a positive (histamine 10%) and a negative control. The test was considered positive if the mean diameter of the wheal was at least 3 mm greater than the negative control test after 15–20 min. Atopy was defined as the presence of at least one positive skin test response. Serum total IgE levels were measured for all patients by nephelometry (Beckman Coulter Immage 800) in all patients.

Metabolic Measurements. Total cholesterol, high-density lipoprotein, low-density lipoprotein, triglyceride and glucose and insulin levels were measured in a fasting blood sample. C-reactive protein (CRP) levels were measured in all patients. The degree of insulin resistance (IR) was estimated by the homeostasis model assessment, HOMA-IR, a valid method for IR estimation in children and adolescents [21]. The HOMA-IR index was calculated by multiplying fasting plasma glucose (mmol/l) by fasting serum insulin (mU/l) and dividing this by 22.5.

Statistical Analysis

The data was analyzed using the SPSS-15 statistical software package (SPSS, Inc., Chicago, Ill., USA). Categorical variables were compared by means of the χ^2 test. Numerical variables were ana-

Table 1. General characteristics of the study groups

Patients	With asthma		Without asthma		p*
	normal weight (n = 49)	obese (n = 52)	normal weight (n = 42)	obese (n = 51)	
Male gender, n	27 (55.1)	31 (59.6)	17 (40.5)	27 (52.9)	0.305
Age (mean $\pm$ SD), years	11.7 $\pm$ 2.4	11.8 $\pm$ 2.4	11.7 $\pm$ 2.9	11.3 $\pm$ 2.4	0.763
BMI	18.7 $\pm$ 2.5	27.7 $\pm$ 3.4	18.6 $\pm$ 2.7	28.3 $\pm$ 4.2	<0.001
MS, n	0 (0)	9 (17.3)	0 (0)	9 (17.6)	0.964
Asthma duration, months	49.3 $\pm$ 30.5	35.6 $\pm$ 27.7	–	–	0.021
Asthma severity, n					
Mild intermittent	21 (42.9)	18 (34.6)	–	–	0.337
Mild persistent	24 (49.0)	27 (52.0)	–	–	
Moderate	3 (6.1)	6 (11.5)	–	–	
Severe	1 (2.0)	1 (1.9)	–	–	
Current ICS use, n	27 (55.1)	31 (59.6)	–	–	0.647
ICS daily dose (median) ^a	400	400	–	–	0.885
Exposure to smoke, n					
Prenatal	5 (10.2)	8 (16.3)	4 (9.5)	5 (9.8)	0.729
Within first year of life	6 (12.2)	12 (23.1)	5 (11.9)	7 (13.7)	0.346
Any secondhand	14 (28.6)	19 (36.5)	16 (38.1)	23 (45.1)	0.433
Allergic rhinitis, n	35 (71.4)	30 (57.7)	–	–	<0.001
Eczema, n	4 (8.2)	2 (3.8)	1 (2.4)	2 (3.9)	0.608
Parental allergic disease ^b , n	20 (40.8)	16 (30.8)	14 (33.3)	15 (29.4)	0.629

Figures in parentheses are percentages. ICS = Inhaled corticosteroid. * p value among the 4 groups.

^a Budesonide or equivalent in micrograms.

^b Parental allergic disease: parental presence of physician-diagnosed asthma and/or allergic rhinitis.

lyzed with one-way ANOVA across all 4 groups and post hoc analysis between 2 groups was performed. Correlations were analyzed using the Spearman's rank correlations. Multiple linear regression analysis was undertaken to determine independent contributors to the dependent variables. $p < 0.05$ was considered significant.

Results

The mean age for the 194 subjects (108 males and 86 females) participating in the study was 11.6 ± 2.5 years. Four independent groups were subsequently identified based on BMI and the diagnosis of the presence of asthma: 2 independent asthmatic groups with ($n = 52$) and without ($n = 49$) obesity, an obese group without asthma ($n = 51$) and a control group with normal weight ($n = 42$). There were 101 subjects with asthma and the asthma severity was classified according to GINA (table 1); of these, 64.3% had allergic rhinitis and 5.9% had eczema (similar to 3.2% among nonasthmatics, $p = 0.504$).

There were no differences among the groups in age, sex, exposure to smoke, the presence of eczema, the pres-

ence of parental allergic disease and the basal FEV₁ (% predicted) levels. The general characteristics and comparison of these groups are presented in tables 1 and 2.

MS was present in 17.5% of the participants who were obese, but not in any of the nonobese children. The prevalence of MS in the asthmatic and nonasthmatic groups ($p = 0.854$) was similar. It was also similar among the obese subjects with or without asthma ($p = 0.964$). In the case of IR, obese subjects had higher mean HOMA-IR levels than nonobese subjects ($p < 0.001$). Obese subjects also had higher levels of serum CRP than nonobese subjects ($p < 0.001$), suggesting an increased systemic inflammation in the obese patients.

Fractional Exhaled Nitric Oxide

FeNO measurements are shown in table 2. There was no significant difference in this level in the 4 groups ($p = 0.093$). When we compared the subjects as asthmatics and nonasthmatics, mean FeNO level did not differ (14.7 ± 8.0 vs. 13.0 ± 5.6 ppb, respectively, $p = 0.078$) between these groups. The mean FeNO level in atopic and nonatopic asthmatics was similar ($p = 0.488$).

Table 2. Laboratory findings of the groups in the study

Variable ^a	With asthma		Without asthma		p*
	normal weight (n = 49)	obese (n = 52)	normal weight (n = 42)	obese (n = 51)	
FeNO, ppb	14.4±8.5	15.0±7.6	11.6±3.9	14.1±6.5	0.093
FEV ₁ predicted, %	97.5±13.7	101.4±15.7	94.9±16.5	97.6±11.3	0.235
Atopy, n (%)	38 (77.6)	35 (67.3)	2 (4.8)	5 (9.8)	<0.001
Total IgE, mg/dl	172.7±264.9	202.2±365.1	39.1±48.8	123.8±270.4	0.035
PB eosinophils, n	279±268	297±383	132±110	173±204	0.009
HOMA-IR	1.8±0.8	2.8±1.5	1.5±0.7	2.9±2.0	<0.001
CRP, mg/dl	0.29±0.42	0.37±0.27	0.24±0.30	0.70±0.74	<0.001
Triglyceride, mg/dl	80.0±29.5	123.3±53.5	88.6±42.9	134.4±57.8	<0.001
HDL, mg/dl	61.4±11.8	48.8±11.8	59.3±12.7	48.9±13.3	<0.001
Total cholesterol, mg/dl	155.8±23.0	169.6±35.4	154.4±22.7	180.6±31.8	<0.001
MS, n (%)	–	9 (17.3)	–	9 (17.6)	0.964

* p value among the 4 groups. HDL = High-density lipoprotein; PB = peripheral blood.

^a Expressed as mean ± standard deviation unless otherwise stated.

When we regrouped all the subjects into 2 groups according to the presence of MS, those with MS had a higher mean FeNO level than those without MS (17.0 ± 8.2 and 13.6 ± 6.8 ppb, respectively, $p = 0.047$). We analyzed the effect of MS on FeNO in asthmatic and nonasthmatic patients separately. Subjects in the asthmatic group with MS did not show a difference in FeNO level when compared to subjects without MS (14.5 ± 8.0 and 16.7 ± 8.7 ppb, respectively, $p = 0.449$). In the nonasthmatic group, subjects with MS had a higher FeNO level than subjects without MS (17.3 ± 8.3 and 12.5 ± 5.1 ppb, respectively, $p = 0.014$).

Spearman's rank correlation coefficients revealed a positive correlation between FeNO level and BMI ($p = 0.049$, $r^2: 0.204$) and CRP level ($p = 0.009$, $r^2: 0.285$) among nonasthmatic patients. However, there was not a significant correlation between FeNO and BMI ($p = 0.239$) or CRP level ($p = 0.080$) among asthmatic patients. There was also a positive correlation between CRP level and BMI ($p < 0.001$ and $r^2: 0.489$), CRP level and HOMA-IR ($p = 0.001$, $r^2: 0.263$) and BMI and HOMA-IR ($p < 0.001$, $r^2: 0.458$).

Univariate and Multivariate Analyses of Factors Associated with FeNO Level

We first performed univariate linear regression analysis to investigate the relation between FeNO level and possible risk factors listed in table 3. We then conducted multivariate regression analysis with the factors with a

p value of <0.25 in order to estimate which factors were independently related to an increased FeNO level. We did not detect an independent risk factor in the asthmatic group; among nonasthmatic subjects, BMI was the sole independent risk factor (table 3).

Discussion

In this study, we aimed to investigate the association of airway inflammation with obesity and its metabolic complications by measuring the FeNO level both in asthmatic and nonasthmatic patients. Although the FeNO level did not differ between obese and normal-weight subjects, the results of this study confirm that there was a positive correlation between BMI and FeNO level in nonasthmatics.

There are conflicting results on the relation between exhaled nitric oxide level and obesity. In some studies, obesity has been associated with a higher [13, 14] as well as a lower FeNO level [15, 22], but a recent study carried out on children did not show a link between FeNO and obesity [16]. De Winter-de Groot et al. [23] hypothesized that obesity might cause pulmonary inflammation, and showed that BMI was positively correlated with FeNO. Similar to these results, Kazaks et al. [24] showed that BMI was positively associated with FeNO in nonasthmatic individuals, but there was no significant relation between FeNO and BMI in people with asthma. Our data also show that BMI is positively associated with FeNO in

Table 3. Univariate and multivariate correlation of factors associated with FeNO

Risk factors	Asthmatic patients			Nonasthmatic patients					
	univariate			univariate			multivariate		
	Beta	CI	p	Beta	CI	p	Beta	CI	p
Age	0.123	1.23–0.22	0.222	0.068	–0.30–0.60	0.518			
Sex	–0.136	–1.36–0.18	0.176	–0.170	–2.53–2.15	0.872			
Secondhand smoke	0.009	0.09–0.93	0.929	0.037	–1.97–2.81	0.726			
ICS daily dose (median) ^a	–0.172	–1.74–0.08	0.085						
BMI	0.081	0.81–0.42	0.420	0.242	0.04–0.41	0.019	0.251	0.03–0.40	0.026
MS	0.076	0.76–0.45	0.449	0.255	1.01–8.65	0.014			
HOMA-IR	0.049	–0.09–1.25	0.638	0.234	0.07–1.46	0.032			
CRP	0.172	1.69–0.09	0.094	0.189	–0.23–3.38	0.087			
Total IgE	0.027	0.26–0.80	0.796	0.018	–0.01–0.01	0.869			
Eosinophil count	0.109	1.08–0.28	0.285	0.147	–0.001–0.01	0.173			
Eosinophil %	0.111	1.09–0.28	0.278	0.127	–0.27–1.07	0.240			
Atopy	–0.069	–0.68–0.49	0.495	0.212	0.19–8.84	0.041			
FEV ₁ predicted	0.031	0.29–0.78	0.781	0.045	–0.07–0.10	0.689			

CI = 95% Confidence interval; ICS = inhaled corticosteroid.

^a Budesonide or equivalent in micrograms.

healthy nonasthmatic subjects. In addition, multivariate regression analyses revealed that BMI is an independent risk factor for an increased level of FeNO after controlling for confounding factors. Despite this link in nonasthmatic subjects, we did not find a link between FeNO and BMI among asthmatic patients and FeNO level did not differ between obese and nonobese asthmatic patients. As there was no difference between obese and nonobese asthmatics in the use of inhaled corticosteroids, this may be related to the presence of background inflammation due to asthma that may conceal the inflammation related to obesity. The absence of a link between FeNO level and obesity in asthmatic patients suggests that the effect of obesity on current asthma might be linked to factors aside from airway inflammation.

In our study, FeNO values did not differ in asthmatic patients and the control group; this is in contrast to previous studies [24, 25]. This may be related to the inhaled corticosteroid use or else to the level of asthma control among our patients (all the asthmatic patients had controlled asthma according to GINA). In contrast, in most of the studies investing the relation between obesity and asthma, the level of asthma control was not considered; indeed, some such studies are carried out in patients with severe or uncontrolled asthma [25, 26].

MS is a severe complication of obesity characterized by hypertension and abnormalities in the metabolism of

glucose and lipids [27]. It is accepted that children with MS are at an increased risk for developing diabetes and cardiovascular diseases, but there are not enough data considering its effect on the respiratory system. A recent study carried out in adults reported a positive independent relationship between MS and lung function impairment [28]. More recently, Ross et al. [29] evaluated the relationship between obesity-related comorbidities and asthma in children and they did not find a link between MS and FeNO level. We also found that, in nonasthmatic subjects, patients with MS had a higher level of FeNO than patients without MS. However, after multivariate analysis, this association did not persist. Our findings did not show a link between MS and FeNO; however, more comprehensive studies are necessary to analyze this.

Obese patients have an increased risk for the development of IR, which is an important component of MS. Several studies have demonstrated a relationship between obesity and asthma, but little is known about the mechanism underlying the relationship between IR and asthma. Recent studies have shown IR to be associated with an increased risk of asthma and asthma-like symptoms [30, 31]. It has also been reported that asthmatic children have a higher HOMA-IR than controls [32]. In our study, HOMA-IR levels did not differ between nonobese asthmatics and healthy controls, and we did not find a correlation between the levels of HOMA-IR and FeNO. In-

deed, the lack of association between IR and FeNO levels suggests that there is no relationship between IR and airway inflammation, but further investigation through prospective studies is necessary in order to draw such a conclusion.

Besides the metabolic complications, several studies have demonstrated persistent low-grade systemic inflammation in obese subjects as shown by higher circulating levels of fibrinogen, TNF α and CRP [26, 33, 34]. In our study, obese subjects had higher serum CRP levels than normal-weight subjects and we found a positive correlation between the levels of CRP and FeNO in nonasthmatics. Even though we did not study other proinflammatory molecules, our findings suggests that high levels of proinflammatory molecules in systemic circulation may contribute to airway inflammation, therefore increasing the possibility of development of asthma in obese subjects.

In this study, we used objective measures of asthma diagnosis, body composition, metabolic parameters and pulmonary functions. The asthmatic group was recruited from a specialty clinic in order to minimize the possibility of the participation of children without asthma. Our study was also strengthened by the inclusion of 2 control groups: were obese and nonobese individuals without asthma. Most of the previous studies on the relation be-

tween obesity and asthma have only considered BMI but not the other related metabolic complications that were examined in this study.

A limitation of this study was that we did not evaluate the airway inflammation by direct methods such as induced sputum or bronchoscopy with bronchoalveolar lavage and biopsy. Such measurements are gold standards for assessing airway inflammation, but their invasiveness and the practical difficulties and costs associated with them make their application impractical. Besides, several studies have reported a significant correlation between FeNO level and eosinophilic airway inflammation in induced sputum, bronchoalveolar lavage and biopsy specimens [35, 36].

In conclusion, we found a correlation between BMI and FeNO level, and the presence of MS seems to be related to an increased FeNO level in nonasthmatic children. Obesity, a well-known risk factor for cardiovascular disease and diabetes, may also be associated with increased airway inflammation which may promote the development of asthma in children. The specific influence of obesity and metabolic abnormalities on asthma is still uncertain, however, and more prospective studies are needed to unravel the underlying mechanism of the relationship between asthma and obesity.

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