

Original article

Cytokine profile of obese asthma phenotype

Background: The incidence of asthma and obesity is increasing worldwide. Understanding the causal directions between asthma and obesity could have important therapeutic implications. However, the mechanism connecting the two is not well defined. **Objective:** This study was undertaken to compare pulmonary function tests (PFTs), C-reactive protein (CRP) and inflammatory cytokines in obesity and asthma in Egyptian adolescents and to investigate whether obese asthmatics have a specific inflammatory phenotype than lean asthmatics. **Methods:** Fifty asthmatic and 30 control subjects were enrolled in the study and divided into 2 sub-groups: obese and non-obese. Serum levels of CRP, leptin, tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), IL-5, body mass index (BMI) and PFTs were done for asthmatics and controls. **Results:** Serum levels of IL-6, TNF- α and leptin in obese individuals whether asthmatic or not showed significant increase compared to lean ones ($P < 0.01$). Body mass index (BMI) showed positive linear correlations with serum levels of IL-6, TNF- α , leptin and CRP. Serum IL-5 showed significantly higher levels in all asthmatics versus all controls ($P < 0.01$). Also serum IL-5 showed non-significant difference between lean and obese asthmatics and it showed significant negative correlations with FEV1/FVC % and PEF. **Conclusion:** Serum levels of IL-6, TNF- α and leptin could be considered surrogate markers for obesity, whereas serum IL-5 is considered a marker of airway inflammation in bronchial asthma. Thus obesity and asthma have been shown to coexist together but systemic and airway inflammation appears to operate independent of each other.

Keywords: Asthma, cytokines, obesity, phenotype.

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INTRODUCTION

The prevalence of obesity (body mass index (BMI) >30 kg/m²) has increased dramatically in the recent decades and it is becoming pandemic worldwide.^{1,2} Asthma is also a major health problem affecting about 300 million people in the world and there may be an additional 100 million persons with asthma by 2025³. The prevalence of bronchial asthma in the Nile Delta region of Egypt was found to be 7.7%⁴.

Numerous epidemiologic studies published during the past decade have demonstrated an increased risk of asthma and asthma-like symptoms in obese individuals with a dose response effect of

increasing BMI on asthma incidence⁵. Furthermore, it is known that obesity may worsen pre-existing asthma, through both biochemical and mechanical effects, and potentially impair response to treatment⁶. In addition, preliminary data suggest that obese patients with asthma demonstrate different asthma phenotypes compared with patients of normal weight⁷.

The adipose tissue was recognized as an active endocrine organ that can affect the function of other organs and as an important source of several proinflammatory cytokines, chemokines, growth factors and adipokines like leptin, adiponectin and resistin⁸. Many adipokines including TNF- α , IL-6, plasminogen activator inhibitor 1, eotaxin, vascular

endothelial growth factor (VEGF) and monocyte chemotactic protein (MCP)-1 have been associated with asthma⁹ and could play a role in the relationship between obesity and asthma. In addition, plasma levels of C-reactive protein (CRP), an acute-phase protein that is elevated in inflammation, and IL-6 levels are both negatively correlated with plasma adiponectin levels¹⁰.

Hence, this study was undertaken to compare pulmonary function tests (PFTs), C-reactive protein (CRP), and inflammatory cytokines in both obesity and asthma in Egyptian adolescents.

METHODS

This study is a cross-sectional, controlled study. A total of 30 healthy controls (16 females and 14 males) and 50 adolescent severe asthmatic subjects (25 females and 25 males) aged 18 years old were evaluated and each was divided into two subgroups using BMI classification¹¹. Asthmatic lean group had 25 patients (13 males and 12 females) with BMI <25.0 kg/m² and asthmatic obese group had 25 patients (12 males and 13 females) with BMI > 30.0 kg/m². Control lean group had 15 subjects (7 females and 8 males) with BMI <25.0 kg/m², and control obese group had 15 subjects (9 females and 6 males) with BMI > 30.0 kg/m². All patients had a clinical diagnosis of allergic severe asthma as follows:

- 1) Reversibility was assessed after administration of 200- 400 µg albuterol by spacer device.
- 2) Atopy was defined as 3 mm greater than control on skin prick testing or detection of specific IgE to one or more of Dermatophagoides Pteronyssinus, grass, trees, cat, dog or Aspragillus fumigates.
- 3) International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma¹²

Informed consents for all participating individuals were obtained. The protocol of the study was approved by the institutional ethical committee.

Patients and controls underwent the following:

- 1- **Specific allergological examination** which included the collection of relevant medical history
- 2- **Body mass index calculation** as weight (Kg)/height (m²).
- 3- **Pulmonary function tests** : forced expired volume in one second (FEV₁), forced vital capacity (FVC), FEV₁/VC and peak expiratory flow (PEF) measured by spirometry (Micro Medical® Spiro USB)

Measurement of serum hsCRP, leptin, TNF-α, IL-5 and IL-6 by ELISA: Peripheral blood was collected from fasting participants in the morning.

Serum levels were determined by using commercially available kits ELISA (DRG ELISA kits, USA).

Statistical Methods

Data were processed and analyzed using the Statistical Package of Social Science (Version 15; SPSS, Inc., Chicago, IL). Normality tests were done using the Shapiro test. The data were presented as mean ± standard deviation (SD). ANOVA test was used to compare the four groups followed by pairwise comparisons using least significant difference (LSD) test. Correlation matrix and coefficient of correlation were done using Pearson's correlation coefficient. Chi-square test and fisher's exact test were used in case of low expected values. A p-value less than 0.05 was taken as the threshold of statistical significance.

RESULTS

Demographic characteristic of the studied groups are shown in table 1.

Analysis of serum levels of IL-6, TNF-α and leptin in the 4 studied groups revealed significantly higher levels (p<0.01) in obese subgroups whether asthmatic or control compared to the lean subgroups (Table 2). Furthermore, serum levels of IL-6, TNF-α and leptin showed a significant positive linear correlation with BMI in the 4 studied subgroups (Table2).

Serum CRP showed significant increase (p<0.01) in asthmatic obese compared to the other 3 subgroups (asthmatic lean, control lean and control obese). Also, it showed significant increase (p=0.04) in asthmatic lean compared to their lean controls (Table 2). In addition, serum CRP showed significant positive linear correlation with BMI in the 4 studied groups (Table 3).

Asthmatic patients whether obese or lean showed significant increase in the mean serum level of IL-5 compared to control obese or lean, whereas non-significant difference was found in serum level of IL-5 between obese and lean asthmatics (Table 2). In addition, significant negative correlations were found between serum IL-5 with all studied parameters of pulmonary function (FEV₁, FVC, FEV₁/FVC ratio, and PEF %) (Table4).

The values of forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), FEV₁/FVC rate, and peak expiratory flow (PEF %) of predicted were found to be significantly lower in asthmatics (lean and obese) than in controls (lean and obese) (p<0.001); however, the lean asthmatics were comparable to the obese ones (Table 5).

Table 1. Demographic characteristic of the studied groups

	Asthmatic Lean		Asthmatic Obese		Control Lean		Control obese		Fisher Exact Test	P value
	No.	%	No.	%	No.	%	No.	%		
Sex										
Female	12	48%	13	52%	7	46.67%	9	60%	0.76	0.90
Male	13	52%	12	48%	8	53.33%	6	40%		
BMI Classification										
Class 1 obesity	0	0%	12	48%	0	0%	2	13.33%	94.33	0.00
Class 2 obesity	0	0%	7	28%	0	0%	5	33.33%		
Class 3 obesity	0	0%	2	8%	0	0%	3	20%		
healthy weight	23	92%	0	0%	15	100%	0	0%		
overweight	0	0%	4	16%	0	0%	5	33.3%		
underweight	2	8%	0	0%	0	0%	0	0%		
Spirometry										
Normal spirometry	0	0%	0	0%	15	100%	15	100%	88.12	0.00
Mild obstruction	7	28%	1	4%	0	0%	0	0%		
Moderate obstruction	3	12%	9	36%	0	0%	0	0%		
Moderately Severe obstruction	6	24%	6	24%	0	0%	0	0%		
Severe obstruction	4	16%	6	24%	0	0%	0	0%		
Very severe obstruction	5	20%	3	12%	0	0%	0	0%		

*Statistical significance was defined as $P \leq 0.05$.

Table 2. Comparison of biochemical parameters of the studied groups

		Serum CRP (mg/l)		Serum Leptin (ng/ml)		Serum TNF- α (pg/ml)		Serum IL-5 (pg/ml)		Serum IL-6 (pg/ml)	
		Mean Difference	P	Mean Difference	P	Mean Difference	P	Mean Difference	P	Mean Difference	P
Asthmatic Lean	Asthmatic obese	-11.85	<0.01	- 23.22	<0.01	-16.30	<0.01	-0.80	0.21	- 27.48	<0.01
	Control lean	2.73	0.04	0.21	0.96	2.11	0.63	3.30	<0.01	8.68	0.06
	Control obese	0.99	0.45	- 22.97	<0.01	-18.75	<0.01	4.04	<0.01	- 26.12	<0.01
Asthmatic Obese	Control lean	14.59	<0.01	23.42	<0.01	18.41	<0.01	4.10	<0.01	36.16	<0.01
	Control obese	12.84	<0.01	0.24	0.95	-2.45	0.58	4.84	<0.01	1.36	0.76
Control lean	Control obese	-1.75	0.23	- 23.16	<0.01	- 20.87	<0.01	0.74	0.10	- 34.80	<0.01

*Statistical significance was defined as $P \leq 0.05$.

Table 3. Pearson's correlation coefficient of body mass index (BMI) and serum cytokine levels in all studied subjects.

		Serum CRP (mg/l)	Serum Leptin (ng/ml)	Serum TNF- α (pg/ml)	Serum IL-5 (pg/ml)	Serum IL-6 (pg/ml)
BMI	Pearson's Correlation	0.42	0.68	0.42	-0.01	0.40
	Significance (2-tailed)	<0.01*	<0.01*	<0.01*	0.93	<0.01*

*Statistical significance was defined as $P \leq 0.05$.

Table 4. Multiple linear regressions of the four spirometric values with gender, BMI and serum cytokines in the all the studied subjects

	Gender		BMI		Serum CRP (mg/l)		Serum Leptin (ng/ml)		Serum TNF- α (pg/ml)		Serum IL-5 (pg/ml)		Serum IL-6 (pg/ml)	
	R	P	R	p	R	P	R	p	R	p	R	p	R	P
FEV 1	-0.70	0.49	0.20	0.84	-0.85	0.40	-0.25	0.80	-0.14	0.89	-4.57	<0.001*	0.70	0.48
FVC%	0.37	0.71	0.31	0.76	-0.69	0.49	-0.22	0.83	0.74	0.46	-1.94	0.05*	0.57	0.57
FEV1/FVC %	-0.71	0.40	0.53	0.60	-0.81	0.42	-0.24	0.81	-0.14	0.89	-4.21	<0.001*	0.71	0.48
PEF%	-0.44	0.66	-0.01	0.99	0.07	0.95	0.15	0.88	-0.19	0.85	-4.71	<0.001*	-0.08	0.93

*Statistical significance was defined as $P \leq 0.05$

BMI: Body mass index; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; and PEF: Peak Expiratory Flow.

Table 5. Pairwise comparison of the spirometric variables in the four studied subgroups.

Dependent variable	Subgroup	Subgroup	Mean difference	SE	P value
FEV1 % of Predicted	Asthmatic lean	Asthmatic obese	2.60	4.24	0.54
		Control lean	-36.52	4.89	<0.01
		Control obese	-29.65	4.89	<0.01
	Asthmatic obese	Control lean	-39.12	4.89	<0.01
		Control obese	-32.25	4.89	<0.01
	Control lean	Control obese	6.87	5.47	0.21
FVC% of Predicted	Asthmatic Lean	Asthmatic obese	7.24	4.11	0.08
		Control lean	-16.40	4.74	<0.01
		Control obese	-11.27	4.74	0.02
	Asthmatic obese	Control lean	-23.64	4.74	<0.01
		Control obese	-18.51	4.74	<0.01
	Control lean	Control obese	5.13	5.30	0.34
FEV1/FVC	Asthmatic lean	Asthmatic obese	-2.28	2.53	0.37
		Control lean	-25.01	2.93	<0.01
		Control obese	-19.55	2.93	<0.01
	Asthmatic obese	Control lean	-22.73	2.93	<0.01
		Control obese	-17.27	2.93	<0.01
	Control lean	Control obese	5.47	3.27	0.10
PEF % of Predicted	Asthmatic Lean	Asthmatic obese	-3.04	4.40	0.49
		Control lean	-34.36	5.08	<0.01
		Control obese	-33.23	5.08	<0.01
	Asthmatic obese	Control lean	-31.32	5.08	<0.01
		Control obese	-30.19	5.08	<0.01
	Control lean	Control obese	1.13	5.68	0.84

*Statistical significance was defined as $P \leq 0.05$

FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; and PEF: Peak Expiratory Flow.

DISCUSSION

Asthma and obesity are growing epidemics in the developing and the developed world⁹. Asthma is a syndrome that includes different phenotypes. One phenotype which has been suggested in clinical studies and identified in cluster analyses is that of an "asthma-obesity" phenotype¹³. Furthermore, obesity is a major risk factor for asthma¹⁴. The mechanistic basis for the association between obesity and asthma is not known, although

mechanical, immunological, genetic, epigenetic, hormonal, and environmental pathways have all been proposed. However, systemic inflammation in obesity could up-regulate the asthmatic pathway, and this is modified by the adipokines and other systemic inflammatory markers^{5,13}. Adipose tissue communicates with other organs through releasing important mediators produced by tissue-resident macrophages and adipocytes, including tumor necrosis factor- α (TNF- α), interleukin 6, and leptin.

The presence of excess adiposity therefore provides a consistent stimulus for chronic, low grade systemic inflammation¹⁵.

In our study, serum levels of IL-6, TNF- α and leptin were found to be significantly elevated in obese versus normal-weight individuals whether asthmatic or control. Also, hsCRP was found to be significantly higher in asthmatic obese group than the other 3 groups (asthmatic lean, control lean and control obese) and it was found to be significantly higher in the asthmatic lean when compared with the lean controls. In addition, these biomarkers (IL-6, TNF- α , leptin and hsCRP) have shown a significant positive correlation with BMI in the 4 studied groups. Thus, hsCRP could be considered a surrogate marker for both obesity and asthma; whereas IL-6, TNF- α and leptin could serve as surrogate markers for obesity. Although the values, notably for TNF- α , leptin, and IL-6, were highest in the obese asthmatic group, the differences compared with obese non-asthmatic group were not significant. In the current study, obesity measured by BMI showed significant positive correlation with both CRP and serum levels of IL-6. Since IL-6 is considered an adipocyte derived interleukin⁹, thus adipose tissue could be considered a dynamic factor responsible for the production of a number of inflammatory markers (leptin, TNF- α and IL-6) that contributes to low grade systemic inflammation¹⁵. However, these markers are related to obesity rather than asthma even though the role of most of them in asthma pathogenesis is well defined. Studies to date have shown associations between TNF- α , IL-6, hsCRP and the obese state. Rexrode et al., found that indices of both total and abdominal adiposity were strongly associated with significant increased levels of CRP and IL-6¹⁶. Park et al., reported higher serum concentrations of TNF- α , IL-6, and CRP in obese than in non-obese individuals¹⁷. In addition, TNF- α , IL-6 and CRP levels were found to be positively correlated with adipocyte size¹⁸. Also Canoz et al., found significant increase in serum concentrations of leptin, TNF- α and IL-6 in obese asthma patients than in non-obese asthma patients¹⁹.

It has also been shown that leptin fulfills an important function in stimulating the release of proinflammatory cytokines such as IL-6 and TNF- α by adipocytes²⁰. Leptin enhances the Th1 response, suppresses Th2 pathways, promotes phagocytosis, and proinflammatory cytokine production^{21,22}. Also, current evidence suggests that systemic leptin may be associated with greater asthma prevalence and/or severity. However, its definite role in asthma pathogenesis is still evolving²³.

TNF- α is expressed in and secreted by adipose tissue²⁴. The metabolic effects of TNF- α in obesity have several potential mechanisms such as influencing gene expression, and impairing insulin signaling²⁵. Levels of TNF- α have been found to be significantly higher in obese children and adolescents compared to non-obese subjects^{10,15}. On the other hand, TNF- α contributes to inflammatory response in asthma by different ways. It induces histamine release from human mast cells, potentiates human mast cells cytokine secretion, increases the cytotoxic effect of eosinophils on endothelial cells and is involved in the activation of and cytokine release by T cells. Besides, it increases epithelial expression of adhesion molecules and is a chemo attractant for neutrophils and eosinophils²⁶. Emerging evidence suggests that it may play an important role in severe, refractory asthma²⁷. Increased TNF- α levels in BAL are associated with increased levels of remodeling in patients with asthma and inhibiting TNF- α reduces asthma exacerbation, further suggesting that TNF- α may be related to airway remodeling²⁸. Interestingly, the TNF- α gene lies within the asthma linkage regions on 6p, and several studies have found associations between the 308-G/A polymorphism of the TNF- α gene (TNF, 6p21,3) and both asthma and obesity²⁹⁻³¹.

IL-6 expression by adipose tissue and circulating IL-6 concentrations are positively correlated with obesity. IL-6 contributes to inflammation in obesity by impairing insulin signalling, and suppressing adiponectin production²⁵. Also, it leads to the synthesis of C-reactive protein (CRP), which exacerbates the inflammatory response¹⁹. Multiple cross-sectional studies have identified significantly elevated levels of IL-6 in obese compared to non-obese children and adolescents. On the other hand, IL-6 is involved in the acute-phase and late-phase asthma response and correlates with asthma disease activity¹⁵. IL-6 promotes the differentiation of Th2 cells by enhancing endogenous IL-4 production by CD4 T cells. It promotes IL-13 production which causes mucus hyper secretion by airway epithelial cells and TH-17 differentiation. It also inhibits Th-1 differentiation, blocks T-reg cells activity³² and promotes subepithelial fibrosis in animal models. Hence, it may be a key modulator of airway remodelling in asthma³³. In addition, polymorphisms at the -174 position of the IL-6 gene were found to be associated with both obesity and asthma susceptibility^{34,35}. Thus IL-6 and TNF- α as biomarkers of obesity could add to asthma severity through enhancing airway remodelling.

IL-5 has been recognized as the most specific cytokine in the eosinophil lineage and has been identified as the key common denominator in inflammatory pathways in asthma³⁶. In the current study, serum IL-5 levels were significantly elevated in asthmatic individuals (obese/lean) in comparison to control group (obese/lean) with non-significant correlation with BMI. Although the highest levels occurred in the obese asthmatic group, the differences compared with non-obese subjects with asthma were not statistically significant. Also, IL-5 levels showed a significant negative correlation with FEV₁%. So, IL-5 is markedly correlated with asthma and its severity rather than obesity. It was previously shown that IL-5 deficiency profoundly impairs visceral adipose tissue eosinophil accumulation and results in increased adiposity and insulin resistance³⁷. However, in our study IL-5 was markedly elevated in asthmatic obese group compared to control obese group which could be explained by an add-on effect of asthma in obese patients.

The most consistently reported effect of obesity on lung function is a decrease in the functional residual capacity (FRC) and expiratory reserve volume (ERV)²¹. Spirometric variables, such as FEV₁ and FVC, tend to decrease with increasing BMI. However, the effect is small, and both FEV₁ and FVC are usually within the normal range in healthy, obese adults and children. The FEV₁-to-FVC ratio is usually well preserved or increased. This indicates that the major effect of obesity is on lung volumes, with no direct effect on airway obstruction³⁸.

In the current study, the FEV₁/FVC ratio in obese asthmatics was $61.80 \pm 10.26\%$, thus showing a reduced ratio compared to non-obese asthmatics yet the difference was non-significant. These findings agree with those of, Ramasamy et al.⁹, Scott et al.³⁹ and Lessard et al.⁴⁰.

In conclusion, it is obvious that there was a definite interaction between asthma and obesity, with regards to inflammation. The intensity of airway inflammation could be relatively greater in obese asthmatic patients through increased levels of obesity biomarkers (TNF- α , IL-6, CRP and leptin), suggesting a synergistic effect of obesity on existing airway inflammation. The fact that serum levels of TNF- α , IL-6, and leptin were higher in obese participants compared to those with normal weight while Th-2 related biomarker (IL-5) was markedly higher in asthmatic individuals compared to controls indicate that TNF- α , IL-6, and leptin fundamentally originate from obesity and could better reflect inflammatory activity in obese

individuals; whereas IL-5 is derived mainly from asthma. However, it is difficult to judge whether one or a group of cytokines in isolation are of importance in a particular disease pathogenesis. In all the settings, obesity seems to have complex effects on the pathogenesis of airway disease in asthma. Further large-scale, gene-based studies are required in order to better clarify the relationship between asthma and obesity and to detect different obese-asthma endotypes.

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