Study of the association between obesity, plasminogen activator inhibitor-1, and asthma in preschool children

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Background Asthma and obesity are recognized as pathological conditions characterized by systemic inflammatory state. Plasminogen activator inhibitor-1 (PAI-1) is the most important endogenous inhibitor of tissue plasminogen activator and uro-plasminogen activator and is thus the major physiological inhibitor of both fibrinolysis and plasmin activation.

Purpose To identify the role of PAI-1 in a group of Egyptian obese asthmatic preschool children and to identify some risk factors for simple obesity and asthma, such as age, sex, socioeconomic status, and type of feeding.

Patients and methods This study was a cross-sectional case–control study that was carried out on 90 children attending Foua Hospital for health insurance in Kafar Elsheikh and Alzahraa University Hospital from September 2015 to March 2017.

Results The frequency of obese children with asthma of high socioeconomic level was higher (63.3%) in comparison with nonobese children with asthma and controls. The prevalence of patients with asthma living in urban areas was higher than those living in rural areas (66.7%). Children who received artificial feeding are more frequent in asthmatic obese (66.7%) when compared with asthmatic nonobese and controls. PAI-1 had significant increase in asthmatic obese (1549.24±340.54) in comparison with other groups.

Conclusion Asthmatic obese children are more frequent among high socioeconomic level and in urban areas. PAI-1 is significantly higher in asthmatic obese than asthmatic nonobese children.

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Introduction

Bronchial asthma is defined as a chronic inflammatory disease of the air passages, typically seen with varied and recurring symptoms, bronchospasm, and reversible airflow obstruction, and symptoms include coughing, wheezing, tightness in the chest, and shortness of breath [1].

Obesity is a major risk factor for asthma; it is thought that inflammatory changes in adipose tissue in obesity cause airway inflammation [2].

Adipose tissue is known to release a number of cytokines including tumor necrosis factor-α, interleukin-6, adiponectin, resistin, eotaxin, transforming growth factor B, C-reactive protein, and leptin, which have been shown to modulate local or systemic metabolism [2].

Plasminogen activator inhibitor-1 (PAI-1) may promote the development of asthma by regulating airway remodeling airway hyperresponsiveness and allergic inflammation [3].

In general, obesity may worsen asthma control; therefore, obese children as well as their parents should be motivated to reduce body weight [4].

Patients and methods

This was a cross-sectional case–control study that was carried out on 90 children aged between 2 and 6 years, attending Foua Hospital for health insurance, in Kafar Elsheikh, and Alzahraa University Hospital, from September 2015 to March 2017. They were divided into the following three groups:

(1) Group I: 30 children with asthma with simple obesity (as defined by GINA, guidelines criteria [5] and WHO [6]).
(2) Group II: 30 asthmatic nonobese children diagnosed asthmatic patients according to GINA, guidelines criteria [5].
(3) Group III: 30 apparently healthy children with matched age and sex were taken as a control group.

Exclusion criteria

The following were the exclusion criteria:

(1) Children below 2 years and above 6 years.

(2) Children with any respiratory disorder other than asthma or chronic diseases such as heart failure, GERD, recurrent aspiration, and chronic infection.
(3) Secondary obesity (e.g., endocrinal disorders).

All studied children were subjected to the following:

(1) Complete history taking (according to a predesigned questionnaire with stress on disease onset, use of controllers, residence, and socioeconomic data to classify it either mild, moderate, or severe).
(2) Thorough clinical examination.
(3) Laboratory investigations [complete blood count, absolute eosinophilic count (AEC), and PLA-1].

Ethical consideration

This study was approved by ethical committee of Al Azhar University.

Statistical analysis [7]

Data were fed to a computer and analyzed using IBM SPSS software package, version 20.0. (IBM Corp., Armonk, New York) [8]. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, SD, and median. Significance of the obtained results was judged at the 5% level.

Results

Table 1 shows that the mean age of the control group was 4.35±1.08 years. The group comprised 17 (56.7%) males and 13 (43.3%) females. Moreover, seven (23%) children had low social level, 18 (60%) moderate, and five (16.7%) high.

The mean age of the asthmatic obese patients was 4.30 ±1.08 years. There were 15 males and 15 females, with 11 (36.7%) children of moderate socioeconomic level and 19 (63.3%) of high socioeconomic level.

The mean age of asthmatic nonobese children was 4.02 ±0.96. There were 15 (50%) males and 15 (50%) females, with six (20%) with low social level, 16 (53.3%) moderate, and 16 (26.7%) high.

Regarding residence, our study showed that prevalence of patients with asthma who lived in urban areas was higher than those who lived in rural (66.7%), whether obese or nonobese.

Table 1 Comparison between the studied groups according to sociodemographic data

	Obese asthmatic (*N*=30) [*n* (%)]	Nonobese asthmatic (*N*=30) [*n* (%)]	Control (*N*=30) [*n* (%)]	Test of significance	*P*
Sex					
Male	15 (50.0)	15 (50.0)	17 (56.7)	χ^2=0.356	0.837
Female	15 (50.0)	15 (50.0)	13 (43.3)		
Age (years)					
<5	18 (60.0)	20 (66.7)	18 (60.0)	χ^2=0.378	0.828
>5	12 (40.0)	10 (33.3)	12 (40.0)		
Minimum–maximum	3.0–6.0	3.0–6.0	3.0–6.0		
Mean±SD	4.30±1.08	4.02±0.96	4.35±1.08	*F*=0.891	0.414
Median	4.25	4.0	4.0		
Socioeconomic					
Low	0 (0.0)	6 (20.0)	7 (23.3)		
Moderate	11 (36.7)	16 (53.3)	18 (60.0)	χ^2=19.265*	^{MC}P<0.001*
High	19 (63.3)	8 (26.7)	5 (16.7)		
Residence					
Urban	20 (66.7)	20 (66.7)	16 (53.3)	χ^2=1.491	0.469
Rural	10 (33.3)	10 (33.3)	14 (46.7)		

MC, Monte Carlo. *p*-value is statistically significant.

Table 2 Comparison between the studied groups according to types of feeding and age of weaning

	Obese asthmatic (*N*=30) [*n* (%)]	Nonobese Asthmatic (*N*=30) [*n* (%)]	Control (*N*=30) [*n* (%)]	Test of significance	*P*
Feeding					
BF	10 (33.3)	16 (53.3)	23 (76.7)	χ^2=11.379*	0.003*
AF	20 (66.7)	14 (46.7)	7 (23.3)		
Age of weaning					
4 months	9 (30.0)	13 (43.3)	11 (36.7)	χ^2=1.148	0.563
6 months	21 (70.0)	17 (56.7)	19 (63.3)		

AF, artificial feeding.

Table 3 Comparison between the two studied asthmatic groups according to severity of asthma and peak-flow spirometer

GINA classification	Obese asthmatic (*N*=30) [*n* (%)]	Nonobese asthmatic (*N*=30) [*n* (%)]	Test of significance	*P*
Classification				
Mild	4 (13.3)	10 (33.3)		
Moderate	8 (26.7)	12 (40.0)	χ^2=7.218	0.027*
Severe	18 (60.0)	8 (26.7)		
Type of controllers				
ICS (fluticasone)	8 (26.7)	19 (63.3)	χ^2=8.148	0.004*
ICS/LABA (fluticasone/salmeterol)	22 (73.3)	11 (36.7)		
Duration of treatment (months)				
Minimum–maximum	3.0–24.0	6.0–24.0		
Mean±SD	14.6±9.21	13.0±7.23	*U*=437.0	0.840
Median	12.0	12.0		
Peak-flow spirometer				
600 ml/s	26 (86.7)	16 (53.3)		
900 ml/s	3 (10.0)	13 (43.3)	8.892*	0.007*
1200 ml/s	1 (3.3)	1 (3.3)		

ICS, inhaled corticosteroids

Table 4 Comparison between the studied groups according to plasminogen activator inhibitor-1 and absolute eosinophilic count

Investigation	Obese asthmatic (*N*=30)	Nonobese asthmatic (*N*=30)	Control (*N*=30)	*H*	*P*
Plasminogen activator inhibitor 1 pg/ml					
Minimum–maximum	893.28–2241.18	92.44–1552.94	94.14–344.54		
Mean±SD	1549.24±340.54	217.96±260.0	160.23±56.54	58.205*	<0.001*
Median	1631.09	184.45	147.48		
Significance between groups	P_1<0.001*, P_2=0.456, P_3<0.001*				
Absolute eosinophilic count					
Minimum–maximum	8.0–15.0	8.0–14.0	2.0–3.80		
Mean±SD	11.40±2.01	10.77±1.83	2.35±0.55	61.117*	<0.001*
Median	11.0	10.50	2.0		
Significance between groups	P_1<0.001*, P_2<0.001*, P_3=0.405				

Table 5 Relation between plasminogen activator inhibitor-1 and different parameters in obese asthmatic group (*N*=30)

	N	Plasminogen activator inhibitor-1			*U*	*P*
		Minimum–maximum	Mean±SD	Median		
Family history of asthma						
No	6	1136.1–1800.0	1516.1±290.4	1581.5	70.500	0.938
Yes	24	893.3–2241.2	1557.5±357.1	1631.1		
Family history of other atopic diseases						
No	6	1136.1–1800.0	1516.1±290.4	1581.5	70.500	0.938
Yes	24	893.3–2241.2	1557.5±357.1	1631.1		
Family history of obesity						
No	12	893.3–1800.0	1391.7±317.0	1445.4	62.000	0.051
Yes	18	1136.1–2241.2	1654.3±321.9	1682.8		
Frequent exacerbation of asthma						
No	6	1136.13–1777.31	1497.619±275.7	1577.31	106.0	0.803
Yes	24	893.28–2241.18	1562.15±358.9	1631.09		
Peak-flow spirometer (three balls test)						
600 ml/s	26	893.3–2241.2	1521.7±352.7	1600.0	30.000	0.519
900 ml/s	3	1506.7–1777.3	1652.7±136.5	1674.0		
1200 ml/s	1#		1954.6			

Table 2 shows that most of obese children with asthma (66.7%) received Artificial Feeding (AF) in comparison with other groups, with significant difference (P<0.5). Moreover, 56.7% of nonobese children with asthma were exclusively breastfed for first 6 months of life.

Table 3 shows that there was a significant increase of severity of asthma and use of Inhaled Corticosteroids (ICS) in obese patients with asthma in comparison with nonobese children with asthma. Moreover, it shows that there was a significant reduction in peak expiratory volume in

Table 6 Relation between plasminogen activator inhibitor-1 and different parameters in nonobese asthmatic group (*N*=30)

	N	Plasminogen activator inhibitor-1			*U*	*P*
		Minimum–maximum	Mean±SD	Median		
Family history of asthma						
No	9	100.8–1552.9	352.5±453.3	210.9	48.500*	0.037*
Yes	21	92.44–344.5	160.3±64.73	127.7		
Family history of other atopic allergy						
No	9	100.8–1552.9	352.5±453.3	210.9	48.500*	0.037*
Yes	21	92.44–344.5	160.3±64.73	127.7		
Family history of obesity						
No	30	92.44–1552.9	218.0±260.0	184.5	–	–
Yes	0	–	–	–		
Frequent exacerbation of asthma						
No	14	100.0–252.94	164.88±51.77	161.76	106.0	0.803
Yes	16	92.44–1552.9	264.39±351.33	186.14		
Peak-flow spirometer (three balls test)						
600 ml/s	16	100.0–1552.9	261.8±347.9	192.44	81.500	0.324
900 ml/s	13	92.44–344.5	166.1±81.07	127.7		
1200 ml/s	1		190.8			

Table 7 Correlation between plasminogen activator inhibitor-1 with different parameters in each group (*N*=60)

	Plasminogen activator inhibitor-1			
	Obese asthmatic		Nonobese asthmatic	
	r_s	*P*	r_s	*P*
Age (years)	–0.332	0.073	–0.050	0.794
Height (cm)	0.307	0.099	0.425*	0.019*
Weight (kg)	0.529*	0.003*	0.372*	0.043
BMI (kg/m^2)	0.574*	0.001*	0.364*	0.048
Classification	–0.052	0.784	–0.029	0.879
Duration (years)	–0.206	0.276	0.100	0.601
Absolute eosinophilic count	–0.048	0.802	0.105	0.424

r_s, Spearman's coefficient. *Statistically significant at *P* value less than or equal to 0.05.

obese patients with asthma than nonobese patients with asthma.

Table 4 shows significant increase in PAI-1 in obese patients with asthma (1549.24±340.54) in comparison with other groups.

Moreover, there was a significant increase of the AEC in obese patients with asthma (11.40±2.01) in comparison with other groups.

Table 5 shows that there was a nonsignificant relation between PAI-1 and all studied parameters.

Table 6 shows that there were significant relations between PAI-1 and positive family history of asthma or atopic allergy.

Table 7 shows significant positive correlations between PAI-1 and height, weight, and BMI in nonobese children with asthma and positive correlations only with weight and BMI in obese children with asthma.

Discussion

The adipose tissue is considered as an active metabolic and endocrine organ, as it is a main source of PAI-1, but not all body fat depots contribute to PAI-1 in an equal manner [9]. PAI-1, the most important physiological inhibitor in endogenous fibrinolysis, is increased in obese patients. This increase may be responsible for the progressive alteration of fibrinolytic activity that occurs with the increasement of weight [10,11].

PAI-1 belongs to the family of serine protease inhibitors (SERPINs). It is a fast-acting inhibitor of fibrinolysis, which alters the balance between thrombosis and fibrinolysis in favor of vascular occlusion [12].

This was a cross-sectional case–control study that was carried out on 90 patients in preschool age (2–6 years). They were divided into three groups: 30 were asthmatic obese, 30 patients were asthmatic nonobese, and 30 normal control children.

The aim of this work was to identify the role of PAI-1 in the obese children with asthma and to identify some risk factors for obesity and asthma such as age, sex, socioeconomic status, and type of feeding.

Regarding the results of the present study, socioeconomic status among studied cases showed that asthmatic obese children were more frequent in

high socioeconomic level (63.3%) compared with other groups. This could be explained by the high socioeconomic level, which allows the chance for more fast unhealthy food consumption.

Drachler *et al.* [13] estimated the relationship between socioeconomic conditions and overweight in infancy, and they found a positive association between socioeconomic level and overweight. However, families with higher socioeconomic status were associated with increased risk of child obesity, as also shown in eastern Algeria.

Regarding residence, our study showed that the prevalence of patients with asthma living in urban areas was more than those living in rural with 66.7%, whether obese or nonobese.

In accordance with our results, Zedan *et al.* [14] reported that the prevalence of asthma was 8%in urban and 7% in rural areas in the Nile Delta region of Egypt.

Moreover, in El-Menofia governorate, Ali *et al.* [15] reported that 14% of urban students and 7.1% of rural students had asthma.

Shaaban *et al.* [16] also reported that the prevalence of patients with asthma living in urban areas (62.2%) was more than rural ones (37.8%). The difference in severity of asthma between urban areas and rural ones is most probably owing to increase in air pollution and increased crowding index in urban than rural areas.

Several observational studies on the allergy-preventive effects of breastfeeding indicate that it is effective for all infants irrespective of family history of allergy. Breastfeeding decreases wheezing episodes in early life; however, it may not prevent development of persistent asthma [17].

Breastfeeding in relation to the development of asthma has been extensively studied, and in general, several studies revealed that infants fed formulas of intact cow's milk or soy protein have a higher incidence of wheezing illnesses in early childhood compared with those fed breast milk [18].

Regarding the types of feeding, our study showed that breastfed infants were significantly higher in control group (76.7%) than obese children (33.3%) and also had less risk of development of asthma and obesity.

Our study also revealed that most of obese children with asthma are those who received formula feeding (66.7%).

Scholtens *et al.* [19] reported in their cohort study on Dutch children that breastfed children had a significantly lower risk of overweight at 8 years. Moreover, Fallahzadeh *et al.*[20] showed a marked lower overweight prevalence among breastfed than non-breastfed children in Iran. Children breastfed for at least 24 months were substantially less likely to be overweight than children breastfed less than 12 months. A longer overall duration of exclusive breastfeeding was associated significantly with a decreased prevalence of overweight.

Obesity may lead to asthma development, and at the same time, asthma may lead to obesity. Despite the apparent link between obesity and asthma, the intrinsic mechanism of their association is unclear [21]. Ciprandi *et al.* [22] demonstrated that obese children tend to have decreased pulmonary volumes while having more bronchial hyperresponsiveness, making them more susceptible to develop asthma symptoms than children who are not obese.

Moreover, Vargas *et al.* [23] who examined the relation of BMI and asthma showed that increasing BMI is associated with increasing incidence of asthma.

Regarding family history, our study showed that most children with asthma had positive family history of asthma, especially obese children with asthma.

This result was in agreement with Burke *et al.* [24] who stated that family history of asthma is common, but it is neither sufficient nor necessary for the development of asthma.

Genetic studies have revealed several candidate genes that have been linked or associated with both obesity and asthma. Obesity candidate genes are clustered in chromosomal regions that have been linked to asthma. Their close proximity may indicate increased potential for inheritance of these two traits simultaneously [25].

Tageldin *et al.* [26] demonstrated that family history of asthma had a major influence on wheeze and asthma in children as most of studied sample (69.9%) had a family member or more with history of bronchial asthma.

Inhaled corticosteroid therapy is available in metered-dose inhalers, in dry powder inhalers, or in suspension for nebulization. Fluticasone propionate, mometasone

furoate, and ciclesonide are used. The selection of the initial ICS dose is based on the determination of disease severity. For the best outcomes, regular daily controller treatment should be initiated as soon as possible after the diagnosis of asthma [17].

Our study showed that there was significant increase of severity of asthma and use of ICS (controllers) in asthmatic obese patients in comparison with asthmatic nonobese.

This is also in accordance with Tavasoli *et al.* [27] who showed a linear relationship between asthma severity and BMI. Moreover, Cassol *et al.* [28] found in their study on children in Brazil that there was a positive association between obesity and asthma severity.

However, Hom *et al.* [29] showed that in some groups of patients with asthma (5–10 years), there was no association between the increased BMI and severity of asthma.

This result is in accordance with Peters *et al.* [30] who analyzed patient response to treatment and type of treatment in relation to BMI in 3000 children with asthma and found that children with low BMI respond to treatment with low number of drugs especially ICS and bronchodilator than children with high BMI.

Peak expiratory flow (PEF) monitoring is a simple and inexpensive home-use tools to measure airflow and can be helpful in a number of circumstances. Similar to spirometry in clinics, poor perceivers of asthma can benefit by monitoring PEFs at home to assess their airflow as an indicator of asthma control or problems. PEF devices are generally less sensitive and reliable than spirometry to detect airflow obstruction, such that in some patients, PEF values decline only when airflow obstruction is severe [31].

Our study showed that there was a significant reduction in peak expiratory volume in obese asthmatic patient than nonobese asthmatic. Ciprandi *et al.* [22] demonstrated that obese children tend to have decreased pulmonary volumes while having more bronchial hyperresponsiveness, making them more susceptible to develop asthma symptoms than children who are not obese.

PAI-1 is the most important endogenous inhibitor of tissue plasminogen activator and uro-plasminogen activator and is thus the major physiological inhibitor of both fibrinolysis and plasmin activation [32]. Many studies suggest that PAI-1 may promote the development of asthma by regulating airway remodeling, airway hyperresponsiveness, and allergic inflammation [3]. Adipocytes produce and secrete PAI-1, and serum levels of PAI-1 are increased in the obese and decrease with weight loss [33].

Increased serum PAI-1 predispose toward hyperresponsiveness of the airways. Obesity-related increase in PAI-1 could provide such an imbalance by enhancing fibrin deposition and by inhibiting the formation of plazmin, a major activator of matrix [32].

Regarding mean serum level of PAI-1, our study showed that PAI-1 had significant increase in asthmatic obese group (1549.24±340.54) in comparison with other groups, asthmatic nonobese (217.96±260.0) and controls (160.23 ±56.54)). This results agreed with Lee *et al.* [34] who reported that levels of PAI-1 are increased in patients with recurrent wheeze in comparison with controls.

Moreover, Cho *et al.* [35] demonstrated that in the lung tissue of patients with asthma, the number of PAI-1 positive mast cell is increased than controls suggesting that PAI-1 expression is elevated in patients with asthma. In another study, Xiao *et al.* [36] reported that in many lung diseases including cystic fibrosis, COPD, and asthma, the plasma level of PAI-1 was increased in comparison with healthy controls.

There was a relation between PAI-1 and weight, height, and BMI in obese children. Most previous studies had reported elevated PAI-1 in obesity [37]. Akanji *et al.* [38] found a positive correlation between PAI-1 and obesity in Kuwait children.

Eosinophils accumulate at sites of allergic inflammation and play important roles in the pathophysiology of asthma through the release of a variety of inflammatory mediators, including major basic protein, cysteinyl leukotrienes, radical oxygen species, and cytokines resulting in bronchoconstriction, mucous secretion, and structural damage to the airways. Response of individuals to treatment with an anti-IL-5 antibody such as mepolizumab raised the eosinophils role in asthma [39].

Regarding AEC in our studied cases, it showed statistically significant increase in children with asthma compared with controls and in asthmatic obese children compared with asthmatic nonobese children.

This is in agreement with Kumar *et al.* [40] who reported that AEC has been found to correlate with clinical severity of asthma. Moreover, elevated AEC in

blood samples of children with asthma was demonstrated in several studies.

EL-Zohery *et al.* [41] found that Egyptian individuals with asthma, with severe attacks had significantly ($P<0.05$) higher AEC than those with moderate attacks and normal group.Moreover, Fulkerson and Rothenberg [42] mentioned that eosinophils are markedly increased in number in blood and airways, with statistically significant increase in children with asthma compared with healthy controls. In agreement with our study, Khakzad *et al.* [43] also reported that patients with asthma showed significantly high numbers of blood eosinophils than control group ($P<0.001$).

Similar to our results, Heffler *et al.* [44] observed that the peripheral blood eosinophil counts in patients with severe asthma were significantly higher than in those with mild asthma.

A family history of atopy is the most clearly defined risk factor for atopy and asthma in children. The strongest association is with maternal atopy, which is an important risk factor for the childhood onset of asthma and for recurrent wheezing that persists throughout childhood [45].

Regarding the relationship between PAI-1 and atopy, our study showed that patients with positive family history of atopy have high levels of PAI-1.

Most studies suggest an association between obesity and asthma, such a relationship has been convincingly demonstrated between obesity and atopy. As atopy is a risk factor for the development of asthma, it is of interest whether obesity increases atopy via inflammatory cytokines.

Because asthma and atopy, cluster in families, they are likely to be powerful genetic factors that predispose toward the development of asthma through gene–environment interactions at specific times as the disease develops and becomes consolidated [46].

These results are supported by Bröms *et al.* [47] who stated that positive family history of asthma was a risk factor for asthma.

Conclusion

(1) Asthmatic obese children are more frequent among high socioeconomic level.
(2) Asthmatic obese children are more frequently prevalent in urban in comparison with rural area.
(3) Breastfeeding decrease the risk of asthma as well as obesity.
(4) There is a significant increase of severity of asthma of those obese patients with asthma in comparison with nonobese children with asthma.
(5) PAI-1 is significantly higher in asthmatic obese than asthmatic nonobese children.
(6) There is appositive correlation between PAI-1, weight, and BMI in obese children with asthma.
(7) Further studies to reveal the mechanisms of PAI-1 expression and action may lead to the development of a novel prognostic factor and the therapeutic target for the treatment and prevention of asthma.

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Conflicts of interest
There are no conflicts of interest.

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