Possible Role of Plasminogen Activator Inhibitor-1 in Childhood Bronchial Asthma

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ABSTRACT

Background: Plasminogen activator inhibitor (PAI)-1 is the main inhibitor of the fibrinolytic system and is known to play an essential role in tissue remodeling. Chronic asthma may lead to tissue remodeling such as subepithelial fibrosis and extracellular matrix deposition in the airways. However, the role of PAI-1 in bronchial asthma is unknown. Our objective is to investigate the correlation between plasma activator inhibitor-1 and childhood bronchial asthma severity, and whether steroid medications could affect its level. The present study included 40 asthmatic children divided into 2 groups (20 patients in each); the asymptomatic group (controlled asthma) where patients were free of symptoms and the symptomatic group, where patients were suffering from acute exacerbation of their asthma and sub-classified into mild and moderate subgroups, each of 10 patients according to severity of acute exacerbation compared to 20 healthy non-asthmatic, age and sex matched. All patients were subjected to full history taking, thorough clinical examinations, peak expiratory flow rate estimation, laboratory investigating: CBC, total serum Ig E, stool analysis and estimation of plasma PAI-1. There was a significant increase of PAI-1 in all asthmatic groups in comparison to control group. The moderate subgroups (A symptomatic and symptomatic) showed highly significant increase in comparison to mild subgroups. On the other hand, there was no significant difference between mild asymptomatic and symptomatic or moderate subgroups to each other. Also there was a significant decrease in PAI-1 levels in patients receiving inhaled corticosteroids than those not receiving inhaled corticosteroids. We conclude that PAI-1 may play an important role in the pathogenesis of asthma and further studies may lead to the development of a novel therapeutic target for the treatment and prevention of asthma.

Key words: Bronchial asthma – Plasminogen activator inhibitor-1
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INTRODUCTION

Asthma represents a chronic inflammatory process of airways. Irreversible air way structural changes characterized by extracellular matrix deposition, subepithelial fibrosis, smooth muscle hypertrophy, and hyperplasia of goblet cell in the airways, known as airway remodeling [1].

Tissue remodeling involves two distinct processes: Physiologic or regeneration, which is the replacement of injured tissue by same type of parenchymal cells, and pathologic which leads to altered restitution of air way structure as increase in smooth muscle and mucous gland mass, with subepithelial fibrosis[2].

Some patients with asthma showed an inefficacy of anti-inflammatory therapy, suggesting that the unregulated pathologic tissue remodeling occurs in spite of adequate anti-inflammatory treatment[3,4]. In recent years, there

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have been major advances in asthma understanding and treatment. A more understanding of disease mechanisms through basic science research has resulted in development of highly specific treatments. These treatments target the dysregulated immune processes of asthma [5].

Plasminogen activator inhibitor-1 (PAI-1) is the key inhibitor of plasminogen activation system, it comprises an inactive proenzyme, plasminogen which can be converted to active enzyme, plasmin. Plasmin degrades fibrin into soluble fibrin degradation products, so PAI-1 down – regulates fibrinolysis [6].

The role of PAI- 1 in asthma is poorly understood, in spite of its known important role in other tissue repair processes as pulmonary fibrosis and renal fibrosis[7,8].

The aim of our present work is to investigate the correlation between PAI-1 and bronchial asthma severity and whether steroid therapy could affect its level.

MATERIALS AND METHODS

The study was performed on two asthmatic groups each included 20 patients attending in Allergy Outpatient Clinic, Children Hospital, Cairo University. The asymptomatic group patients were free of symptoms (controlled asthma) and sub-classified into mild and moderate persistent subgroups each of 10 patients according to asthma severity; they were 11 males and 9 females with age ranged from 4-12 years. The symptomatic group (uncontrolled asthma) patients were suffering from acute exacerbation of their asthma and sub-classified into mild and moderate subgroups according to severity of acute exacerbation; they were 14 males and 6 females with age ranged from 4-13 years. The study also included 20 healthy non-asthmatics, age and sex matched controls. Patients with any underlying lung pathology as a cause of wheezing complicated with infections and those found to have parasitic infestations were excluded from the study.

All patients were subjected to: detailed history taking, thorough clinical examinations, chest x-ray to exclude any disease other than bronchial asthma, peak expiratory flow rate (PEFR) readings, baseline pulmonary function tests (mainly FEV_1), laboratory investigations (CBC including absolute eosinophilic counts, total serum IgE level by micro particle enzyme immune-assay technique, urine and stool analysis) and estimation of plasma PAI for patients and controls using ELIZA technique (American Bioproducts Parisppany' NJ).

Statistical Methods:
All the above data were collected and statistically tested by analysis of variance or students't-test. Correlations were studied by simple Persons Coefficient. Significance was defined as P<0.05.

RESULTS

A total number of 60 children (33 males and 27 females) were included in this study, they were divided into 3 groups; control group included 20 non-asthmatic children (11 males and 9 females) their age ranged between 2.6 to 12 years (mean ± SD. 6.79±2.65 years). A symptomatic group included 20 asthmatic children and classified into mild and moderate subgroups each of 10 children. In mild subgroup there were 6 males and 4 females with age ranged between 4.5 to 12 years (mean ± SD: 5.55±2.27 years). In moderate subgroup there were 4 males and 6 females with age ranged between 4 to 8 years (mean ± SD: 5.45±1.38 years). Symptomatic group included 20 asthmatic children suffering from acute exacerbation of their asthma and subclassified into mild and moderate subgroups each of 10 children. In mid subgroup, there were 6 males and 4 females with age ranged between 4 to 11 years (mean ± SD: 5.65±2.22 years). In moderate subgroup, there was 6 males and 4 females with age ranged between 4 to 13 years (mean ± SD: 8.2±3.17 years).There was no significant difference between the study groups as regards age and sex.

Table (1): Shows the results of absolute eosinophilic count (AEC) in all studied groups, where AEC ranged between 0-530/mm³(163.45±154.77/mm³) incontrol group, between 0-570/mm³(253.6±194.31/mm³) in mild asymptomatic, between 0-345/mm³(161.0±107.37/mm³) in moderate asymptomatic, between 55-756/mm³(315.2±248.38/mm³) in mild symptomatic, between 0-590/mm³(242.2±214.0/mm³) in moderate symptomatic subgroup. There was no significant difference between the study groups as regards AEC.

Table(2): Shows the results of total serum IgE in all studied groups, where IgE levels ranged between 12.0-107.0 IU/dL (53.7±27.35 IU/dL) in control group. In mild asymptomatic IgE level ranged between 288-1560 IU /dL (910±392.51 IU/dL) and in moderate asymptomatic between 168-1339 IU/dL (803.8±369.1 IU/dL).

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In mild symptomatic it ranged between 197-2303 IU /dL (1025.7±524.10 IU/dL) and in moderate symptomatic subgroup it ranged between 662-2571 IU/dL (1699.08±704.62 IU/dL).

There was a highly significant elevation in serum IgE of the asthmatic groups than control group. No significant difference was found between asymptomatic subgroups (mild and moderate) and mild symptomatic subgroups, while the moderate symptomatic subgroup showed highly significant elevation in total IgE levels in comparison to other asthmatic subgroups.

Table (3): Shows the overall results of plasminogen activator inhibitor -1 in all studied groups. In control group PAI-1 levels ranged between 8 to 42 ng/mL (20.1±12.52 ng/mL). In mild asymptomatic PAI-1 ranged between 44-55 ng/mL (48.3±6.27 ng/mL). While moderate asymptomatic ranged between 44-70ng/mL (56.1±7.03 ng/mL).

In mild symptomatic, PAI-1 levels ranged between 44-65 ng/mL (50.3±8.02 ng/mL) and between 59-65 ng/mL (61.80±2.09 ng/mL) in moderate symptomatic subgroup. There was significant more mean values of PAI-1 in all asthmatic groups compared to control group. Moderate subgroups (asymptomatic and symptomatic) showed highly significant increase compared to control group and to both mild asthmatic subgroups. No significant difference between mild subgroups and also no significant difference between both moderate subgroups.

Table (4): Shows comparison between patients receiving inhaled corticosteroids (ICS) and those not receiving ICS as regards levels of PAI-1, where there was a significant lowering in patients receiving ICS.

Table (1): Comparison of AEC (Cell/mm³) in all studied groups

AEC (Cell /mm³)		Mean ± SD	Rang	Sig.
Control gr.		163.45 ± 154.77	(0 :530)	
Asymptomatic group.	Mild	253.6 ± 194.31	(0 :570)	0.17
	Mod.	161 ± 107.37	(0 : 345)	0.964
Symptomatic group	Mild	315.2 ± 248.38	(55: 756)	0.06
	Mod.	242.2 ± 214.58	(0 : 590)	0.258

Table (2): Comparison of serum total IgE (IU/dL) between all studied groups

IgE (IU/dL)	F test	6.13			
	Sig.	0.00*			
Tukey test	Mild Asymptomatic	Moderate asymptomatic	Mild symptomatic	Moderate symptomatic	Control
Mild Asymptomatic		0.097	0.97	0.001*	0.00*
Moderate Asymptomatic	0.97		0.75	0.006*	0.00*
Mild Symptomatic	0.97	0.075		0.00*	0.00*
Moderate Symptomatic	0.00*	0.006*	0.00*		0.00*
Control	0.00*	0.00*	0.00*	0.00*	
Mean ± SD	910±392.51	803.8±369.18	1025.7±524.10	1699.8±704.62	53.7±27.35

Table (3): Comparison of serum PAI-1 (ng/mL) in all studied groups

PAI	F	36.84			
	Sig.	0.00*			
Tukey test	Mild Asymptomatic	Moderate asymptomatic	Mild symptomatic	Moderate symptomatic	Control
Mild Asymptomatic		0.00*	0.794	0.00*	0.001*
Moderate Asymptomatic	0.00*		0.00*	0.221	0.00*
Mild Symptomatic	0.794	0.00*		0.00*	0.001*
Moderate Symptomatic	0.00*	0.221	0.00*		0.00*
Control	0.001*	0.00*	0.001*	0.00*	
Mean ± SD	48.3±6.27	56.1±7.03	50.3±8.02	61.8±2.09	20.1±12.52

Table (4): Comparison of serum PAI-1 (ng/mL) in patients receiving inhaled corticosteroids (ICS) and those not receiving ICS

PAI-1	Range	Mean ± SD	Sig.
ICS N = 10	(8 : 56)	19.30 ± 16.546	0.00*
Non ICS N = 30	(20 : 70)	45.80 ± 12.826	

DISCUSSION

Asthma is a complex disorder, which cannot be defined adequately in terms of a universally comprehensive and acceptable definition. However, many definition have been proposed; The National Heart, Lung and blood Institute, international asthma consensus report National Asthma Education Program Expert Panel Report II (1997), regarded

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asthma as a chronic inflammatory airway disorder in which many cells play a role especially eosinophils and mast cells[9].

Asthma may have its onset at any age. 10-15% of boys and 7-10% of girls may have asthma during childhood. About 80-90% has their first symptoms before 4-5 years of age and 30% of them are symptomatic by one year of age[10].

PAI-1 is approximately 52.000 Mr., single chain, cysteine-less glycoprotein which is released by endothelial cells, macrophages, monocytes, hepatocytes, platelets and adipocytes[11]. PAI-1 is induced in airways by viral infections and may mediate airway remodeling[12].

In our study there is significant increase of mean value of PAI-1 in all asthmatic groups in comparison to control healthy subjects and the moderate asthmatic subgroups showed highly significant increase of mean value of PAI-1 compared to mild subgroups.

Both mild subgroups (Asymptomatic and symptomatic) showed no significant difference to each other but are significant with lower mean values to moderate subgroups and a higher mean value to control groups.

Moderate subgroups showed no significant difference to each other but significant higher mean value to mild subgroups.

The above mentioned results indicate that with bronchial asthma have increased fibrinolytic activity and PAI-1 down-regulates fibrinolysis in the circulation[6]. PAI-1 may prevent fibrosis not only by inhibiting migration of inflammatory cells but also by promoting the plasmin-dependent pathway[13].

Similar to our results, Liu et al. (2016), Stewart et al. (2013) and Huang et al. (2013) suggest that the PAI-1 inhibitor may have therapeutic potential for asthma by suppressing eosinophilic allergic response and ameliorating airway remodeling[14,15,16].

In our study the level of PAI-1 is increased with increased degree of asthma severity, which is similar to the result of CHO et al. (2016) whom concluded that a genetic variant of PAI-1 together with early life lower respiratory infections as RSV bronchiolitis within the first 2 years of life is a associated with increased risk of asthma morbidity and reduced lung functions[12].

Also Malmstrom K et al. (2011) and Cho S et al. (2011), reported that PAI-1 was negatively associated with FVC in patients with asthma[17,18].

In our present study we have compared PAI-1 in patients using inhaled corticosteroids (ICS) with those not using, where we found that patients used ICS had statistically significantly lower mean value compared to those not using ICS (19.3±16.546 ng/mL vs. 45.8±12.826 ng/mL) with highly significant value.

PAI-1 mRNA increased 3-fold in the cultured murine keratinocytes after the addition of 1 UM hydrocortisone by 2 hours and remained elevated for at least 8 hours[19].

There is evidence that bronchial hyper-responsiveness to methacholine, asthma symptom score and inflammatory cells, decreased significantly after both low and high dose of fluticasone propionate. Moreover the remodeling features of the airwayas increase in the vascularity area, increase in number of vessels, and the basement membrane thickness, decreased only after high dose of fluticasone propionate[4,20].

In our present study, there is highly significant lower mean value of PAI-1 in patients using ICS compared to those not using ICS. This means that the use of ICS enhances fibrinolytic activity and promotes extracellular matrix degradation in patients with bronchial asthma. Also, our study confirms the fact that ICS in very low dose of corticosteroids could prevent airway remodeling in asthma compared to use of high dose corticosteroid as concluded by the study done by. Baraket et al. (2012)[4].

CONCLUSION

 PAI-1 may play an important role in the pathogenesis of asthma and further studies evaluating the mechanisms of PAI-1 action in asthma may lead to the development of a novel therapeutic target for the treatment and prevention of asthma.

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