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ORIGINAL ARTICLE

Serum Periostin as a Diagnostic and Prognostic Marker in Bronchial Asthma either Atopic or Infection Induced

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ABSTRACT

Background: Asthma is a persistent bronchial tree disorder characterized by inflammation of the airway that is completely or partially reversible, which can intensify naturally or subside only after direct treatment. Airway hyperactivity is defined as the reduction of the airways as a response to a variety of stimuli. This study aimed to assess the role of serum periostin in diagnosis of asthmatic children and its relation to asthma etiology either atopic or infective.

Method: A prospective Cross-sectional study was carried out at pulmonology unit of Pediatric Department, at Zagazig University hospitals from December 2016 to January 2018. Forty six-patients diagnosed as bronchial asthma were recruited in the study and full history and clinical examination were taken. Full lab was taken such as complete blood count, C reactive protein, erythrocyte sedimentation rate, IGE level and Serum periostin. Pulmonary function tests (PFTs) were performed with spirometer. Statistical analysis was done for these data.

Results: Serum periostin was significantly higher in asthmatics and in patients with uncontrolled compared to controlled asthma. It was significantly higher in those with severe and moderate asthma than those with mild asthma. Significant negative correlation between serum periostin level and pulmonary function parameters were detected. A logistic regression analysis showed that serum periostin level was predictor of impaired forced expiratory volume 1 (FEV1) in asthmatic children.

Conclusions: The study proved that serum levels of periostin, a new biomarker, were higher in asthmatic children. increase level of serum perostin in uncontrolled asthma and severe asthmatic attack.

Keywords: Bronchial Asthma; Abnormal Periostin Level; Abnormal PFTs

INTRODUCTION

Asthma is a heterogeneous, multifactorial disease based on a chronic inflammatory bronchial reaction with variable and mostly reversible obstruction of the respiratory pathway. Symptoms (cough, wheezing, tightness of the chest or shortness of breath) vary and are correlated with the limitation of expiratory flow[1]. Asthma is the most common chronic childhood disease and the leading cause of chronic disease infant morbidity as measured by school absences, visits to emergency departments, and hospitalizations. Asthma also starts in early childhood in as many as half of patients with asthma [2]. During the healing process following myocardial infarction and the growth of multiple tumors, periostin was recognised in the development of bone, teeth and heart valves. Periostin also took part in atopic diseases such as dermatitis and rhinitis/ rhinosinusitis [3]. It is especially essential for the onset of inflammation, specifically for allergic inflammation. Periostin is a matricellular protein stored in fibrosis-inflamed areas, while it stimulates immune and non-immune cells [4]. Serum periostin used as a biomarker of asthma remodeling may result in its association with inhaled corticosteroid (ICS) hyporesponsiveness. Many clinical studies have shown that serum periostin is high in ICS-resistant patients with asthma, especially in eosinophilic groups and high periostin asthma. [5]. Serum periostin levels in patients with high doses of ICS (> 1000 mg daily) were significantly higher, suggesting that serum periostin may be a biomarker of eosinophilic airway inflammation that is at least partially refractory to ICS [6]. This study aimed to assess the role of serum periostin in diagnosis of asthmatic

children and its relation to etiology either atopic or infective.

PATIENTS AND METHODS

A prospective Cross sectional study was carried out at pulmonology Unit Pediatric Department, Zagazig University Hospitals from December 2016 to January 2018. Forty-Six patients diagnosed as bronchial asthma were enrolled for this study, a written informed consent was taken from all the patients before the start of the study, we measured pulmonary function test for all children at the day of admission, and serum perostin measured by ELISA. The largest percentage of patients studied ranged from 5 to 14 years of age for males.

The thesis was accepted by the Faculty of Medicine's ethical review committee at Zagazig University. The work was carried out for human studies in accordance with the World Medical Association's Code of Ethics (Helsinki Declaration).***Inclusion criteria*** were children diagnosed as bronchial asthma were from both sexes with age range from 5-18 years, recurrent attack of wheezy chest**.** ***Exclusion criteria*** were patients with chronic chest disease problems other than bronchial asthma, any neurologic, cardiac, upper airway troubles interfering with PFT technique, and interstitial lung diseases were excluded from this study.***Methods:*** Each Patient is subjected to complete history taking including personal, present history taking presenting symptoms, the age of onset, the duration of disease, triggering factors, frequency and severity of acute exacerbation, presence of night symptoms, persistent symptoms in between the attacks, limitation of physical activity, history of other allergies, frequency of rescue medication, type of controller therapy, response to medication. past history of disease, drug, operation and recurrence, Asthma predictive index. Complete examination for patients which is done for assessment of body systems including general examination for vital signs measurement. Also detailed Chest examination was done with recording of auscultation findings and signs of respiratory distress, Abdomen examination was done.***Investigations:*** routine laboratory investigation as complete blood count (CBC), blood eosinophil, total immunoglobulin E (IgE), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), kidney function tests (KFT), and liver function tests (LFT) were done and other investigations as Chest X ray, and PFTs.

Blood samples from 8:00 a.m. to 9:00 a.m. The Shino test (Kanagawa, Japan) used an enzyme-linked immunosorbent assay to measure periostin levels.[7] ***Pulmonary function tests***: Pulmonary function tests were assessed on the day after admission, during remission and relapse. Spirometer-based pulmonary function screening (2010 Ganshorn, Medizin Electronic GmbH Industries, Trasse 6-8, 97618, Nieder Lauer, Germany). Computer version LF 8.5) to calculate the forecast forced vital power (FVC), the forecast forced expiratory volume (FEV1) and its ratio (FEV1/FVC) Normal physiology was defined by all predicted measurements of > 80%, a restrictive defect as a reduced (< 80% predicted) FVC with a FEV1/FVC ratio of > 70% predicted or reduced DLCO (< 80% predicted), and an obstructive defect as a reduced FEV1 with a normal FVC and a low FEV1/FVC ratio (< 70% predicted). Small airway disease was described as reduced FEV1 (< 70% forecast), low FEV1/FVC (< 70% forecast) and reduced MEF25–75 (< 60% forecast) [8].

Statistical analysis :SPSS version 15 (SPSS, Inc., Chicago, IL, USA) was used to do statistical analysis. Continuous data as average and distance are conveyed. Continuous and categorical variables have been tested using the Mann – Whitney U-test and the Yates modification chisquare test where applicable. Using Kruskal – Wallis H-test, intergroup analysis of more than two variables was carried out. The correlation coefficient of Spearman or Pearson was used to determine the relationship between the two continuous variables based on the data distribution. All P values were based on a 2-tailed distribution, and the corresponding P value; Non-significant (NS) difference if P > 0.05. Significant(S) difference if P < 0.05. Highly significant (HS) difference if P< 0.001.

RESULTS

Group CharacteristicsAge of the studied patients ranged from 5 to 14 years with a mean 8.66 years, Male constituted 56.5% of them. About 59% of patients lived in urban areas and 58.7% of them had Positive family history of asthma. **Table (1)** Twenty-eight patients had infection induced asthma. Cough followed by dyspnea represented the most common complaints. About 15% and 10% had moderate persistent and severe persistent asthma respectively. About 57% of patients had well controlled asthma. Nineteen patients (41.3%) had no controller and fourteen patients (30.5%) received leukotriene antagonist (LTRA). **Table (2)** FEV1 of the studied patients ranged from 64 to 89% with mean 78.96% and FEV1/FVC of the studied patients ranged from 70 to 98% with mean 80.33% as shown in **table (3).** There is significant positive correlation between serum periostin and both total leucocytic count, eosinophil count, CRP, ESR, and IgE. There is no significant negative correlation between serum periostin and platelet count. There is significant negative correlation between serum periostin and both FEV1, FVC and FEV1/FVC as shown in **table (4).** There is

statistically significant relation between serum periostin level and asthma type (non-significantly higher in infection-induced asthma). There is statistically significant relation between serum periostin level and asthma severity. On LSD comparison, the difference is significant between intermittent asthma and each other type, and between mild asthma and each other type. There is statistically significant relation between serum periostin level and asthma control. On LSD comparison, the difference is significant between each two individual groups as shown in **table (5)**

Scatter dot graph showing significant negative correlation between serum periostin level and FEV1/FVC as shown in **figure (1)**.

The best cutoff of serum periostin in diagnosis of severe persistent asthma among the studied patients is ≥ 131.5 ng/ml with area under curve 0.944, sensitivity 87.5%, specificity 92.1%, Positive predictive value (PPV) 60%, Negative predictive value (NPV) 97.2%, positive likelihood ratio 11.1, negative likelihood ratio 0.14 with accuracy 89.1% (p<0.001) as shown in **figure (2).**

Table (1): Distribution of the studied patients according to demographic characteristics:

	N=46	%
Age (years)		
Mean ± SD	8.66 ± 2.11	
Range	5 - 14	
Gender:		
Male	26	56.5
Female	20	43.5
Residence:		
Rural	19	41.3
Urban	27	58.7
Family history:		
Negative	19	41.3
Positive	27	58.7
Body weight:		
Overweight	6	13.
Average	37	80.4
Underweight	3	6.5
History of other allergies:		
Negative	32	69.4
Positive	14	30.4

Table (2): Distribution of the studied patients according to disease specific characteristics:

Disease specific characteristics	N=46	%
Type of asthma:		
Infection-induced	28	60.9
Atopic	18	39.1
Complaint:		
Cough	17	37
Dyspnea	11	23.9
Cough, dyspnea	2	4.3
Dyspnea and wheezes	6	13
Cough, dyspnea and wheezes	10	21.7
Severity:		
Intermittent	19	41.3
Mild persistent	15	32.6
Moderate persistent	7	15.2
Severe persistent	5	10.8
Level of control:		
Uncontrolled	11	23.9
Partially controlled	9	19.6
Well controlled	26	56.5

Disease specific characteristics	N=46	%
Controller :		
ICS high dose	6	13
ICS moderate dose	10	21.7
ICS low dose	8	17.8
LTRA	14	30.5
No	19	41.3

Table (3): Distribution of the studied patients according to Spiro metric characteristics:

	Mean ± SD	Range
FVC	98.06 ± 5.55	85.33 -110
FEV1 (%)	78.96 ± 7.41	64 – 89
FEV1/FVC (%)	80.33 ± 6.92	70 - 98

Table (4): Correlation between serum Periostin level and age, laboratory data and spirometric measures among the studied patients:

Parameters	serum Periostin level	
	r	p
Age (years)	-0.005	0.974
Hemoglobin level (g/dl)	0.227	0.129
TLC (10^3/mm^3)	0.374	0.01*
Eosinophil	0.893	<0.001**
Platelet count (10^3/mm^3)	0.117	0.439
CRP (mg/dl)	0.884	<0.001**
ESR (mm/hour)	0.912	<0.001**
IgE	0.869	<0.001**
FVC (%)	-0.372	0.011*
FEV1 (%)	-0.744	<0.001**
FEV1/FVC (%)	-0.588	<0.001**

r: Spearman correlation coefficient **p≤0.001 is statistically highly significant

Table (5:) Relation between serum periostin level and some disease specific characteristics of the studied patients:

Variables	Serum periostin level		Test	
	Mean ± SD	Median (Range)	Z/F	p
Type:				
Atopic	76.62 ± 45.25	72 (34-155)	-1.363	0.173
Infection-induced	93.97 ± 40.8	88.5 (38.4-160)		
Severity:				
Intermittent	50.35±10.92	24 – 72		
Mild persistent	87.44 ± 8.33	68 – 95		
Moderate persistent	123.19 ± 26.82	88 – 156.33	F=103.8	<0.001**
Severe persistent	142.78± 10.76	130 - 146		
Control:				
Un controlled	136.5±13.97	118 – 156.33	F=57.78	<0.001**
Partially controlled	112.73 ± 29.18	88 – 160		
Well controlled	59.3 ± 18.18	34 - 92		

Z: Mann Whitney test, F: One Way ANOVA, **p≤0.001 is statistically highly significant

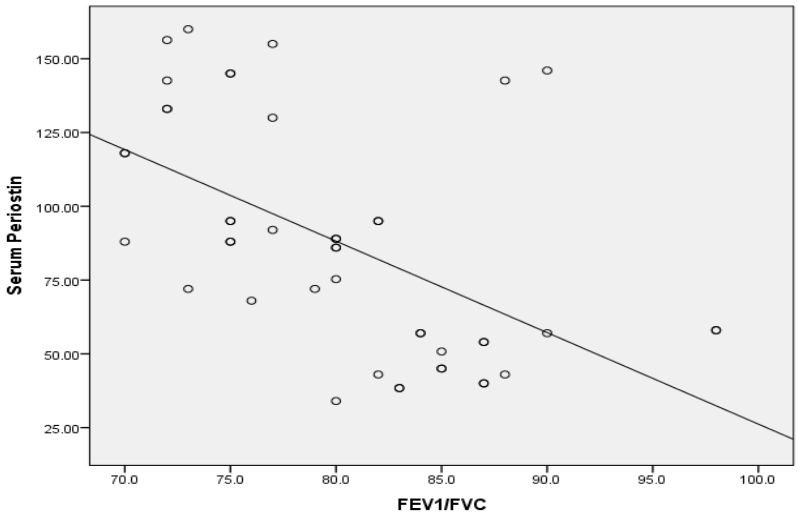

Figure (1): Scatter dot graph showing significant negative correlation between serum periostin level and FEV1/FVC

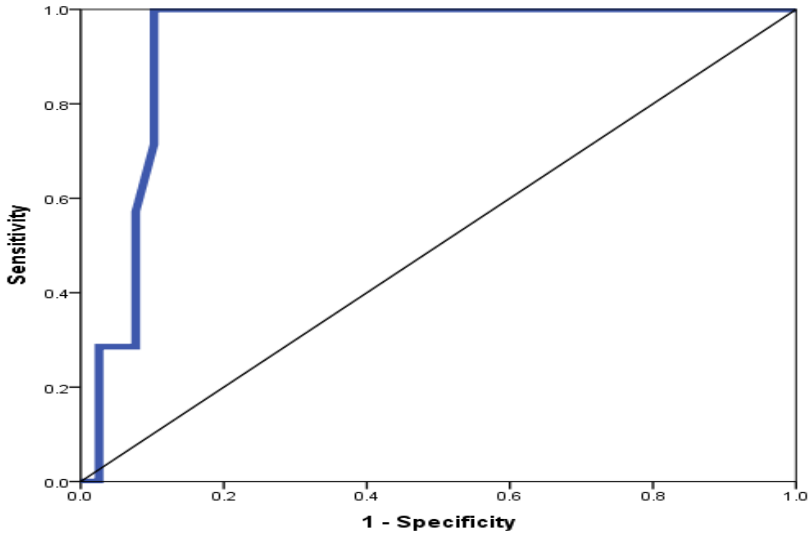

Figure (2): ROC curve showing performance of serum periostin in diagnosis of severe persistent asthma

DISCUSSION

Asthma is a chronic bronchial tree disorder characterized by a completely or partially reversible obstruction of the airway that can improve spontaneously or only subside after specific therapy. Airway hyperresponsiveness is characterized by airway narrowing as a response to a range of stimuli, such as allergens and non-specific causes and infections. Asthma is a common disease of children and adults, affecting 300 million people worldwide**.**[9]

Periostin is an extracellular matrix (ECM) protein expressed in fibroblasts or epithelial cells. T-helper cell 2 (Th2) cytokines induce periostin in fibroblasts that is involved in asthma subepithelial fibrosis**.**[7]Especially essential for the onset of inflammation, particularly for allergic inflammation, are the dual functions of periostin as an ECM and a matricellular protein. Periostin is stored in inflamed areas of fibrosis, while it stimulates immune and non-immune cells as a matricellular protein**.**[4]

In some studies, serum periostin is reproductively correlated with eosinophilia, fractional inhaled NO (FiNO) and IgE **(Johansson et al.,** [10]**).** In comparison, serum periostin is associated with aspirin resistance, nasal diseases, and late onset asthma, in which eosinophilic inflammation is often observed, thus confirming periostin's classification as a type 2 biomarker. In addition, cluster analysis showed that high periostin is a trait of the eosinophilic-dominant asthma community.[11]Serum periostin levels in patients with high doses of ICS (> 1000 mg daily) are significantly higher, indicating that serum periostin may be a biomarker for eosinophilic airway inflammation that is at least partially refractory to ICS [6]**.**This study found out that 58.7% of our cases had positive family history of asthma while **Elhady et al.,** [12] reported that most cases (70%) had positive family history of bronchial asthma.

This study showed that (30%) had history of other allergic disorder as allergic rhinitis and skin allergy unlike **Elhady et al.,** [12] who found out that (45%) had history of other allergic disorder.

The present study reported that asthma was mild intermittent (41.3%), mild persistent asthma (32.6%), moderate persistent asthma (15.2%) and severe persistent asthma (10.6%) of our cases. **Song et al.,** [13] studied 54 asthma patients; 14 had mild intermittent asthma, 19 had mild persistent asthma, and 21 had moderate asthma according to the Global Initiative for Asthma (GINA) guidelines.**Casciano et al.,** [14] reported that Forty percent of patients were classified as having mild asthma and 60 % had moderate-to-severe asthma according to study definitions. **Inoue et al.,** [7] reported that 19 patients (67.9%) had mild asthma in the asthma group, nine patients (32.1%) had moderate asthma, and all 28 patients had good control.Our results are in agreement with study of **Kanemitsu et al., [**6] as they reported they Serum periostin levels of asthmatic patients (92.8 6 38.4 ng/mL) were significantly higher than those of healthy subjects (39.1 6 24.5 ng/mL; P < .001). **Takayama et al.,**[15] clearly demonstrated that periostin is deposited in the airway subepithelial layer in asthmatic patients.

Regarding **Inoue et al.,**[7] the mean serum periostin level in the asthma group was 134.0 (116.3–166.3) ng / ml and 112.0 (97.0–132.0) ng / ml in the control group, showing significantly higher periostin serum levels in children with asthma.In the study in our hands, FEV1 of the studied patients ranged from 64 to 89% with mean 78.96%. FEV1/FVC of the studied patients ranged from 70 to 98% with mean 80.33%. The positive correlation between serum periostin and total leucocytic count, eosinophil count, CRP, ESR, and IgE is significant. There is no significant negative association between periostin serum and platelet count or hemoglobin level. The positive correlation between serum periostin and FEV1, FVC and FEV1/FVC is significant.

Our results are in line with study of **Baek et al.,**[16] as they reported that in children with exercise induced asthma, the maximum decreases in FEV1% after exercise was positively correlated with serum periostin levels.

Our results are in agreement with study of **Elhady et al.,**[12] showed a significant negative correlation between serum periostin level and FEV1 in asthmatic children. **Kanemitsu et al.,**[6] high serum periostin concentration (almost 95 ng / ml) was reported to be the unique biomarker among several serum markers associated with the highest annual decline in FEV1 (at least 30 ml / year). Our results are in agreement with study of **Elhady et al.,**[12] as they revealed that serum periostin level was significantly correlated with asthma severity, level of asthma control, blood eosinophilia and impaired pulmonary function. Experimental studies demonstrated that periostin is linked to severe airway inflammation and hyperresponsiveness.**Nair and Kraft.,**[17] displayed a significant increase in serum periostin levels in asthma patients with evidence of eosinophilic inflammation of the airway **Jia et al.,**[18] found that serum periostin is the single best systemic biomarker of airway luminal and tissue eosinophilia in severe, uncontrolled asthmatics with a positive predictive value of 93 %.

Regarding **Kanemitsu et al.,**[6] We found that a higher reduction in FEV1 was correlated exclusively with elevated serum periostin (approximately 95 ng/ mL) (estimated consequence, 25.39; 95% CI, 210.0 to 20.77; P 5.02). Fifty-two patients (23%) showed a 30 mL or greater decline in FEV1 per year (251.8 6 18.4 mL per year) and were considered to be rapid decliners. Lower serum periostin levels at diagnosis, care stage 5, a history of admission attributable to asthma exacerbation, lower daily doses of ICS, comorbid or a history of sinusitis, and ex-smoking are correlated with a reduction in FEV1 of 30 mL or higher per year when balanced by confounders. High periostin serum (average 95 ng/ mL) was also associated with a 30mL or greater decline in FEV1 per year.The present findings were in accordance with **Jodie and colleagues,** [19] **s**tudies who found that the best cutoff value for serum periostin calculated was 90 ng/ml showing a sensitivity of up to 95 with 83% specificity and with a positive predictive value of 95% for predicted asthma control and severity.

CONCLUSIONS

Serum periostin had a significant, sensitive, accurate clinically relevant indicative value as regards asthma control and severity. Serum periostin could not only be a reliable biomarker for eosinophilic inflammation, but can also contribute to the development of airways that reshape IBD activation.The present study has some limitations including small number of patients and this study was based on cross-sectional analysis, so we could not monitor the changes in serum periostin level through the course of the disease or its response to therapeutic interventions. We included children with bronchial asthma mainly depending on their level of control on treatment over the previous 6 months.

RECOMMENDATIONS

Usage of large sample of patient including follow up. Exclusion of other allergic diseases as serum level of perostin may be elevated in other allergic diseases. Measurement of perostin level in sputum compared with serum level.

Conflict of Interest The authors report no conflict of interests.

Financial Disclosures one

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