Journal of Advances in Medicine and Medical Research

32(17): 53-67, 2020; Article no.JAMMR.61525
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Serum Periostin Level in Asthmatic Children with Exercise Induced Bronchospasm

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Authors' contributions

This work was carried out in collaboration among all authors. Author RMS designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors MBH and RMES managed the analyses of the study. Author HAE managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2020/v32i1730642
Editor(s):
(1) Dr. Ashish Anand, GV Montgomery Veteran Affairs Medical Center, University of Mississippi Medical Center and William Carey School of Osteopathic Medicine, USA.
Reviewers:
(1) Juan B. De Sanctis, Palacký University Olomouc, Czech Republic.
(2) Martin Rohacek, University of Basel, Switzerland.
Complete Peer review History: http://www.sdiarticle4.com/review-history/61525

Original Research Article

Received 15 July 2020
Accepted 21 September 2020
Published 26 September 2020

ABSTRACT

Background: There are few biomarkers that can be easily accessed in clinical settings and may reflect refractory Th2-eosinophlic inflammation and remodeling of the asthmatic airways. Serum periostin may be one such biomarker to aid our understanding of the patho-bio-physiology of asthma and exercise induced asthma. The aim of the study is to explore the relationship between serum periostin level and exercise induced bronchoconstriction in asthmatic children.
Materials and Methods: This cross-sectional study was carried out on (90) children both sexes aged from 6 to 15 years including, (60) children with bronchial asthma and (30) children were enrolled as control group in the period from January 2018 to January 2019. Patients were randomly classified into two groups: I) Patient group: divided into 2 groups according to standardized treadmill exercise challenge test: Group A: (30) asthmatic children with positive test. Group B: (30) asthmatic children with negative test. II-Control group: (30) children apparently healthy with no personal or family history of asthma. All children were subjected to the following Investigations: Chest x-ray, pulmonary functions tests (FEV_1 & PEFR) except controls, Laboratory investigations as CBC and Serum periostin level.

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Results: The mean values of both the percentage of PEFR and FEV_1 after exercise in group A were significantly lower than those in group B and the percentage of PEFR and FEV_1 after exercise in each group were significantly lower than the percentage before exercise in the same group. The mean value of eosinophilic count in group A was significantly higher than (group B and control group) and the mean value of eosinophilic count in group B was significantly higher than control group. The mean value of serum level of periostin in group A was significantly higher than (group B and control group), however, there was no significant difference between group B and control group as regard to serum level of periostin.

Chest tightness, cough and wheezes after exercise and eosinophilic count in patients with high serum periostin level were significantly higher than patients with low serum periostin level, and both PEFR and FEV_1 after exercise in patients with high serum periostin level were significantly lower than patients with low serum periostin level. Also the normal serum periostin levels vary among different age groups.

Conclusion: Serum periostin level can be considered as a useful biomarker for diagnosis of Exercise induced bronchospasm (EIB) in asthmatic children especially when lung function test cannot be done However, cautious is required in evaluating serum periostin levels in children because it varies with age.

Keywords: Serum periostin; asthmatic children; exercise; bronchospasm.

1. INTRODUCTION

Exercise induced bronchoconstriction (EIB) describes the transient increase in airways resistance that follows vigorous exercise. Development of EIB has been attributed to repetition of long periods of intense ventilation and concomitant inhalation of pollutants or irritants during numerous training sessions [1]. Dehydration induces increased osmolality of the bronchial surface fluid, triggering the release of mediators by inflammatory cells of the airways, thereby inducing bronchoconstriction in children with bronchial hyper- responsiveness (BHR). Penetration of allergens and pollutants during effort is also facilitated by the intense ventilation induced by exercise [2].

There are few biomarkers that can be easily accessed in clinical settings and may reflect refractory Th2-eosinophlic inflammation and remodeling of the asthmatic airways [3].

Matricellular protein is a recent concept that was coined for an extracellular matrix protein that causes a vicious cycle of inflammation and remodeling. Periostin is one of these matricellular proteins and is upregulated by IL-4 and IL-13 stimulation from airway epithelial cells and other structural cells [4]. T-helper 2 cell (Th2) cytokines induce periostin expression in fibroblasts, which was involved in subepithelial fibrosis in asthma. Significant periostin expression has been noted in the bronchial epithelial cells of children with asthma [5].

Serum periostin may be one such biomarker to aid our understanding of the patho-bio-physiology of asthma and EIB [3].

The aim of the study is to explore the relationship between serum periostin level and exercise induced bronchoconstriction in asthmatic children, and evaluate the ability of periostin for being a non-invasive biomarker for diagnosis of EIB in asthmatic children.

2. SUBJECTS AND METHODS

This cross-sectional study was carried out on (90) children both sexes aged from 6 to 15 years including, (60) children diagnosed with bronchial asthma and (30) children were enrolled as control group in the period from January 2018 to January 2019

Subjects were classified into two groups. I) Patient group: divided into 2 groups according to standardized treadmill exercise challenge test: Group A: (30) asthmatic children with positive test. Group B: (30) asthmatic children with negative test. II) Control group: (30) children apparently healthy with no personal or family history of asthma.

The exclusion criteria include: Patients with conditions that may affect serum periostin levels including those with: chronic diseases other than bronchial asthma such as: (renal disease and heart disease), acute infection, had suffered asthma attack in the last 30 days or with other acute pulmonary disease such as: pneumonia and pneumothorax.

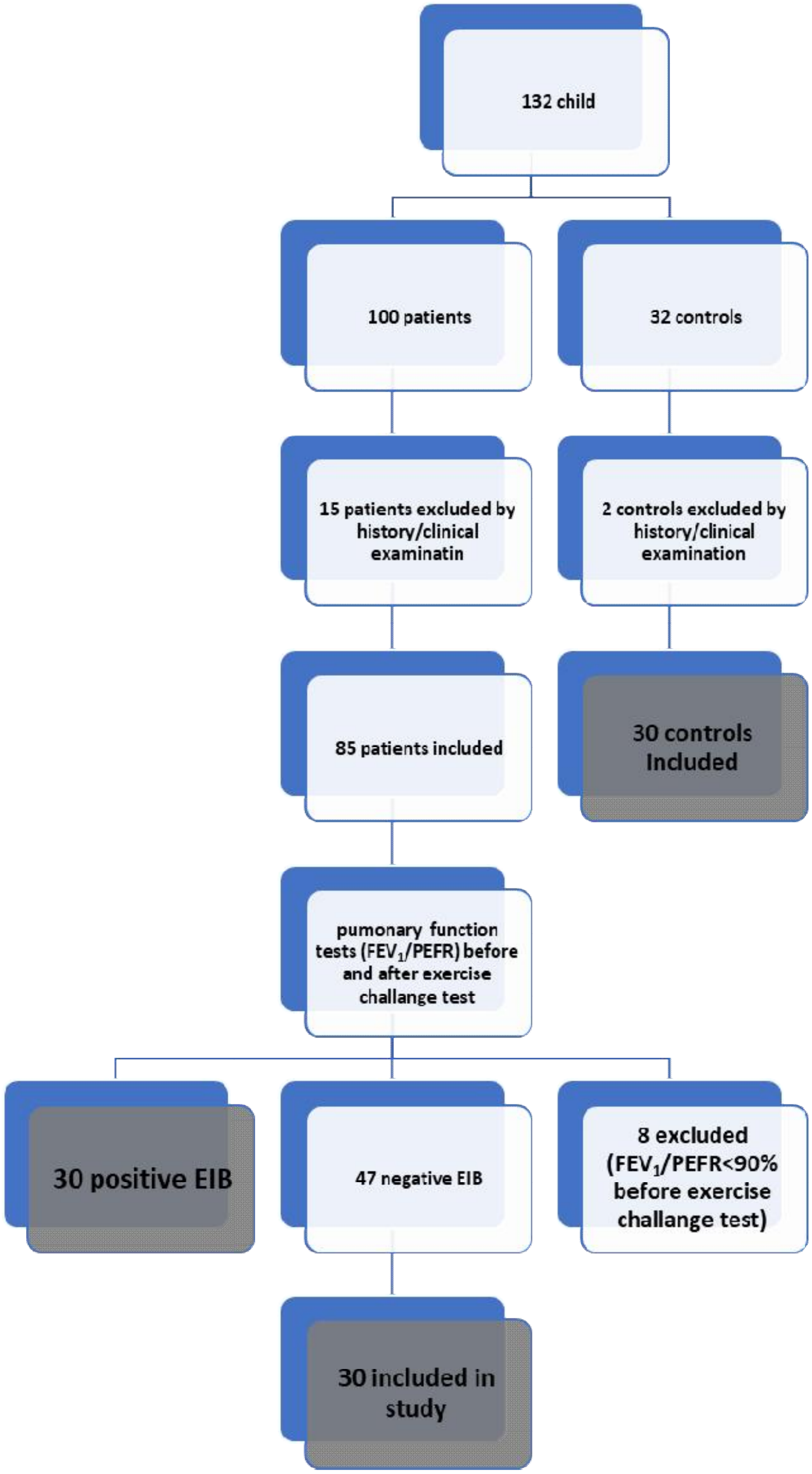

Fig. 1. Stepwise selection of study subjects

After history taking and physical examination of 100 cases and 32 controls, 85 of cases and 30 controls were selected. After that pulmonary function test was done just before standardized treadmill exercise challenge test. From the enrolled 85 controlled asthmatic patients, 8 of them were excluded for being uncooperative then according to the definition of (EIB) as the percent fall in FEV_1 from baseline > or equal 10% within 20–30 minutes after exercise. 30 patients had positive exercise challenge test, and 47 patients had negative exercise challenge test, only 30 of the later were enrolled as a negative group, Fig. (1).

All children were subjected to the following Investigations: Chest x-ray, pulmonary function tests (FEV_1 & PEFR) except controls, Laboratory investigations as CBC with eosinophilic count and serum periostin level.

Five milliliters of random venous blood were collected from each subject under complete sterile conditions, two milliliters were put into vacutainer EDTA tube for CBC, and the rest of blood was put into plain vacutainer tube labeled with patient name. The blood was allowed to clot for half an hour in water path at 37° c then it was centrifuged for 15 minute at 3000 r.p.m for separation of serum by means of clean dry tube for determination of periostin level by enzyme linked immunosorbent assay (ELISA) by using (ELISA) kits, supplied by ELAab. Catalog N: E1767h. Switzerland. The sera of all subjects were stored at -20 c till the time of estimation of serum level of periostin.

2.1 Statistical Analysis

Analysis of data was performed by SPSS v25 (SPSS Inc., Chicago, IL, USA). Quantitative parametric variables (e.g. age) were presented as mean and standard deviation (SD). They were compared between the two groups by unpaired student's t- test, within the same group by paired T test. ANOVA (F test) for normally quantitative variables, to compare between more than two groups, and Post Hoc test (LSD) for pairwise comparisons. Pearson's product correlation coefficient: it evaluates the linear association between 2 quantitative variables value of "r" ranges from -1 to 1. P value < 0.05 was considered significant.

3. RESULTS

Patient flowchart of each step of the trial is shown in Fig. (1). As regards demographic data (age and gender), family history of asthma or atopy, consanguinity and Anthropometric measurements including weight, height, BMI, there were insignificant differences between the studied groups, Tables (1-2).

There was no statistically significant differences between group A and group B as regard to the percentage of PEFR and FEV_1 before exercise (p-value > 0.05), however the mean value of both the percentage of PEFR and FEV_1 after exercise in group A was significantly lower than those in group B and the percentage of PEFR and FEV_1 after exercise in each group were significantly lower than the percentage before exercise in the same group (p-value < 0.05), Table (3).

There were significantly more patients in group A developed cough and chest tightness after exercise in comparison with group B (p-value < 0.05). Also significantly more patients in group A developed chest tightness and wheezes after exercise in comparison with group B (p-value < 0.05), although none of the studied patients in either group A or B had chest tightness or wheezes before exercise, Table (4).

There was no statistically significant difference between studied groups as regard to chest x-ray findings at time of enrollment (p-value > 0.05), Table (5).

The mean value of eosinophilic count in group A was significantly higher than (group B and control group) and the mean value of eosinophilic count in group B was significantly higher than control group (p-value < 0.05), Fig. (2).

The mean value of serum level of periostin in group A was significantly higher than (group B and control group) (p-value < 0.05), however there was no statistically significant difference between group B and control group as regard to serum level of periostin (p-value > 0.05), Fig. (3).

Serum periostin level at a cut off value of >197ng/dl yielded a sensitivity of 96.67% and specificity of 98.33% for diagnosis of exercise induced bronchospasm (EIB) in studied patients, Fig. (4).

There was no statistically significant differences between patients with high and low serum periostin according to cut off value of Roc curve as regard to age, sex and both PEFR and FEV_1 before exercise (p-value>0.05), However chest tightness, cough and wheezes after exercise and eosinophilic count in patients with high serum periostin level were significantly higher than patients with low serum periostin level, and both PEFR and FEV_1 after exercise in patients with high serum periostin level were significantly lower than patients with low serum periostin level (p-value<0.05), Table (6).

Table 1. Demographic data (age and gender), family history of asthma or atopy, consanguinity

T		Range			Mean	±	S. D	F. test	p. value
Age (years)	Group A(n=30)	6	–	15	9.90	±	2.81	0.17	0.83
	Group B(n=30)	6	–	15	9.60	±	2.33		
	Controls(n=30)	6	–	15	9.53	±	2.50		

Sex			**Group A(n=30)**	**Group B(n=30)**	**Controls(n=30)**	**Total**
Male		N	19	19	21	59
		%	63.3%	63.3%	70.0%	65.6%
Female		N	11	11	9	31
		%	36.7%	36.7%	30.0%	34.4%
Total		N	30	30	30	90
		%	100.0%	100.0%	100.0%	100.0%
Chi-square	X^2	0.394				
	P-value	0.821				

Family history of asthma or atopy			**Group A(n=30)**	**Group B(n=30)**	**Total**
Yes		N	16	14	30
		%	53.3%	46.7%	50.0%
No		N	14	16	30
		%	46.7%	53.3%	50.0%
Total		N	30	30	60
		%	100.0%	100.0%	100.0%
Chi-square	X^2	0.267			
	P-value	0.606			

Consanguinity			**Group A(n=30)**	**Group B(n=30)**	**Controls(n=30)**	**Total**
Positive		N	16	8	14	38
		%	53.3%	26.7%	46.7%	42.2%
Negative		N	14	22	16	52
		%	46.7%	73.3%	53.3%	57.8%
Total		N	30	30	30	90
		%	100.0%	100.0%	100.0%	100.0%
Chi-square	X^2	4.737				
	P-value	0.094				

** significant at (p-value < 0.05)*

Table 2. Anthropometric measurements in studied groups

		Range			Mean	±	S. D	F. test	p. value
Weight (kg)	Group A(n=30)	20.0	–	66.0	34.57	±	12.23	0.058	0.943
	Group B(n=30)	20.0	–	62.0	33.83	±	10.17		
	Controls(n=30)	20.0	–	65.0	33.62	±	11.37		
z score of weight for age	Group A(n=30)	-1.51	–	1.16	0.11	±	0.48	1.554	0.217
	Group B(n=30)	0.78	–	0.94	0.25	±	0.39		
	Controls(n=30)	-0.47	–	1.30	0.28	±	0.36		
Height (cm)	Group A(n=30)	116.0	–	173.0	139.20	±	16.77	0.221	0.802
	Group B(n=30)	117.0	–	172.0	137.33	±	12.93		
	Controls(n=30)	116.50	–	175.0	136.77	±	14.51		
z score of height for age	Group A(n=30)	-1.50	–	1.0	0.0	±	0.44	1.412	0.249
	Group B(n=30)	-0.40	–	1.0	0.19	±	0.40		
	Controls(n=30)	-1.10	–	0.80	0.09	±	0.45		
BMI (Kg/m^2)	Group A(n=30)	14.86	–	22.05	17.24	±	1.91	0.128	0.880
	Group B(n=30)	14.08	–	22.10	17.49	±	1.97		
	Controls(n=30)	14.01	–	21.47	17.42	±	1.94		
z score of BMI for age	Group A(n=30)	-1.0	–	0.90	0.11	±	0.52	0.969	0.383
	Group B(n=30)	-1.20	–	1.10	0.27	±	0.55		
	Controls(n=30)	-1.30	–	1.10	0.27	±	0.49		

** significant at (p-value < 0.05)*

Table 3. Comparison of pulmonary function tests before and after exercise in studied patients

			Group A(n=30)	Group B(n=30)	t. test	P_1-value
PEFR (%)	Before exercise	Range	90 – 97	90 – 98	0.013	0.909
		Mean	94.40	94.33		
		SD.	2.36	2.12		
	After exercise	Range	75 – 86	85 – 94	86.977	**0.001***
		Mean	81.23	88.87		
		SD.	3.63	2.64		
P_2-value			**<0.001***	**<0.001***		
FEV_1 (%)	Before exercise	Range	90 – 96	90 – 96	0.078	0.781
		Mean	92.53	92.67		
		SD.	1.96	1.73		
	After exercise	Range	71 – 83	83 – 93	132.544	**0.001***
		Mean	78.43	87.07		
		SD.	3.28	2.48		
P_2-value			**<0.001***	**<0.001***		

t: Student t-test

p_1-value: p value for comparing between the two studied groups.

p_2-value: p value for Paired t-test for comparing between before exercise and after exercise in the same group.

** significant at (p-value < 0.05)*

Table 4. Asthma related manifestations in studied patients

		Group A(n=30)	Group B(n=30)	χ^2	P
Cough					
Before exercise	N	8	6	0.373	0.542
	%	26.7%	20.0%		
After exercise	N	23	6	19.288*	<0.001*
	%	76.7	20.0		
Chest tightness					
Before exercise	N	–	–	–	–
	%	–	–		
After exercise	N	6	0	6.667*	^{FE}p=0.024*
	%	20.0	0.0		
Wheezes					
Before exercise	N	–	–	–	–
	%	–	–		
After exercise	N	9	0	10.588*	0.002*
	%	30.0	0.0		
Shortness of breath					
Before exercise	N	7	2	3.268	^{FE}p=
	%	23.3	6.7		0.145
After exercise	N	20	7	11.380*	0.001*
	%	66.7	23.3		
Total	N	30	30		
	%	100.0%	100.0%		

χ^2: Chi square test FE: Fisher Exact test,
p: p value for comparing between the two studied groups,
**: Statistically significant at p ≤ 0.05*

Table 5. Chest x-ray findings in studied groups at time of enrollment

Chest x-ray findings			Group A(n=30)	Group B(n=30)	Controls(n=30)	Total
No abnormality detected (NAD)		N	21	22	25	68
		%	70.0%	73.3%	83.3%	75.6%
Increased broncho-vascular markings		N	9	8	5	22
		%	30.0%	26.7%	16.7%	24.4%
Total		N	30	30	60	90
		%	100.0%	100.0%	100.0%	100.0%
Chi-square	X^2	1.564				
	^{MC}P-value	0.557				

χ^2: Chi square test MC: Monte Carlo

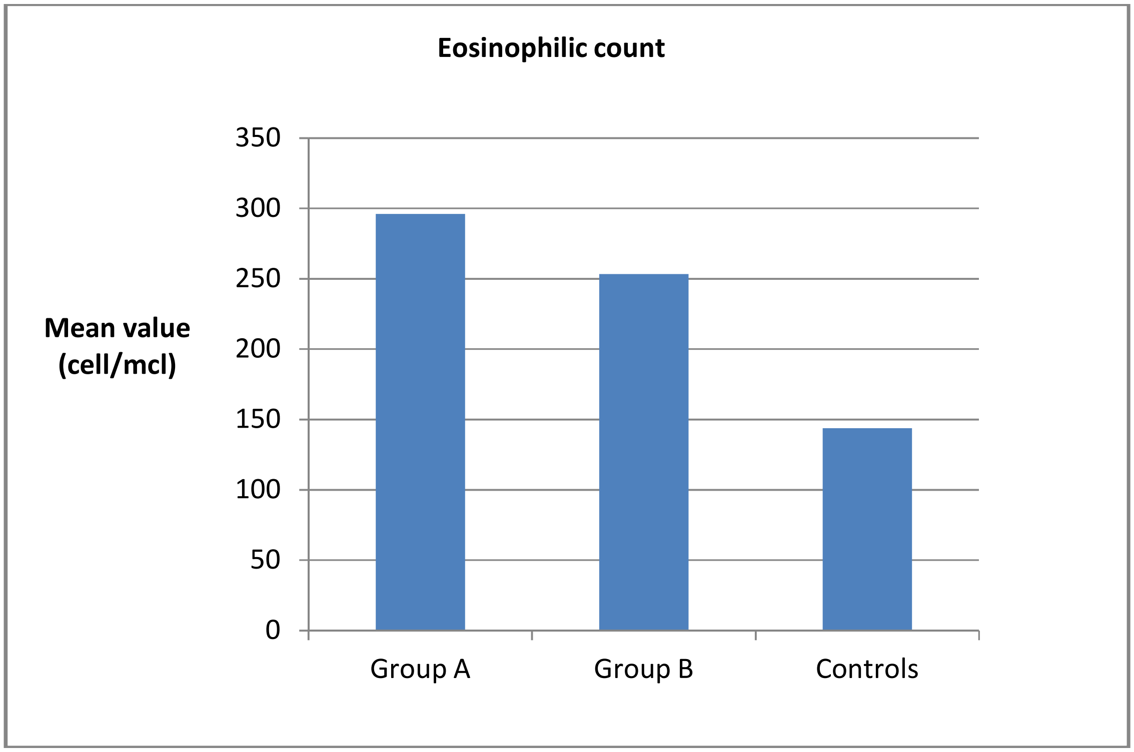

Fig. 2. Eosinophilic count in studied groups at time of enrollment

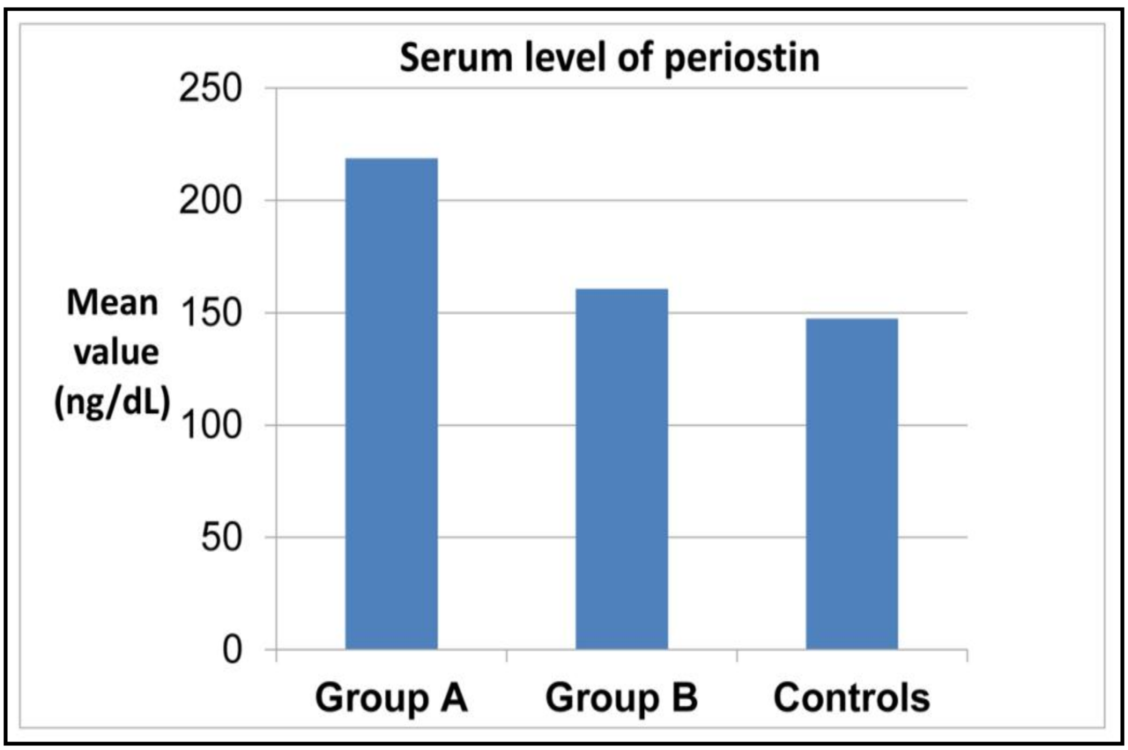

Fig. 3. Serum level of periostin in studied groups

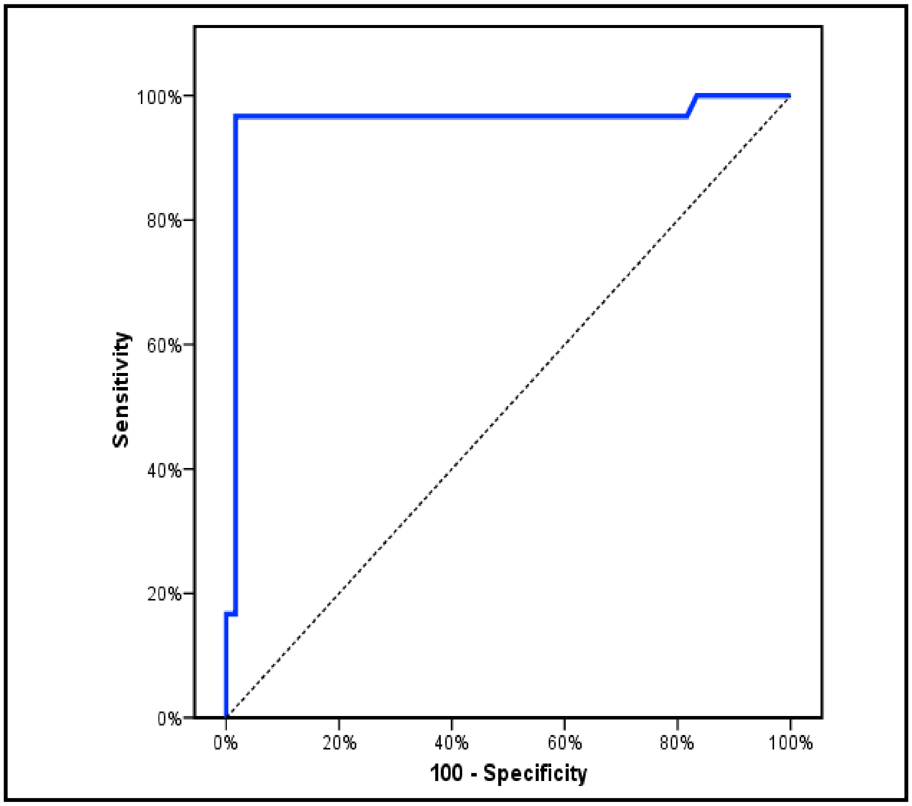

Fig. 4. ROC curve for serum level of periostin to diagnose EIB in studied patients

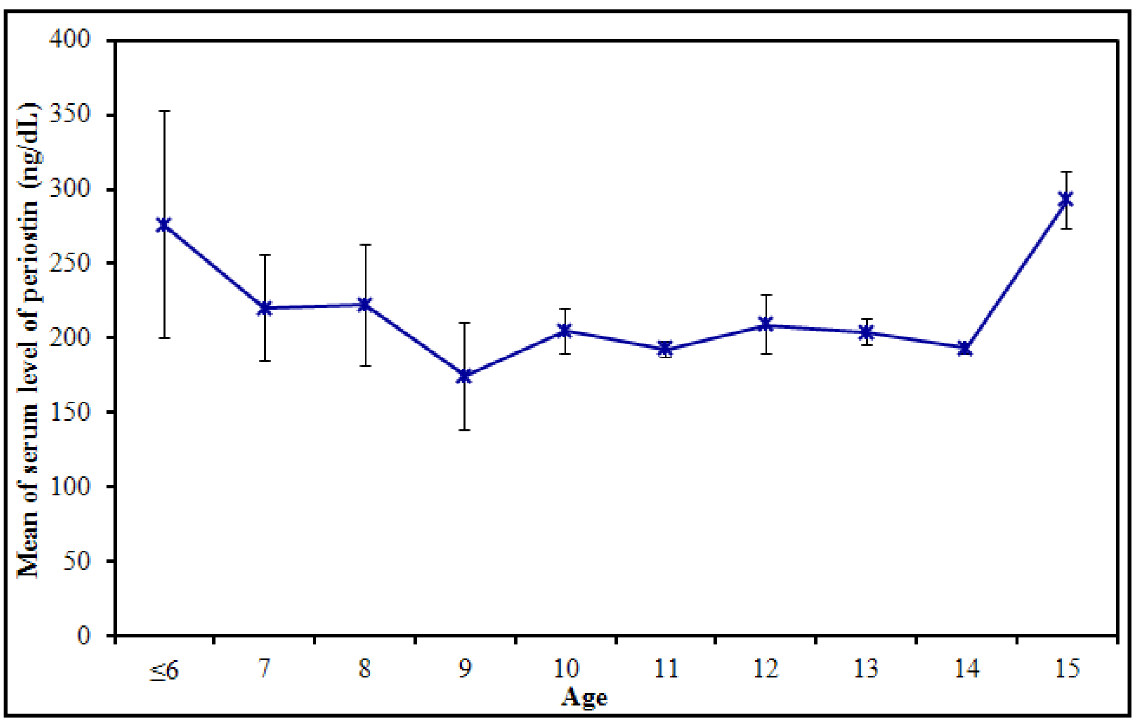

Fig. 5. Relation between age in years and serum level of periostin (ng/dL)

Table 6. Comparison between high versus low level of serum periostin according to cut off value of Roc curve as regard to different parameters

	Serum level of periostin				**Test of Sig.**	**p-value**
	≤179 Low(n = 30)		**>179 High(n = 30)**			
Age (years)						
Min. – Max.	6.0 – 15.0		6.0 – 15.0		t =0.153	0.879
Mean ± SD.	9.73 ± 2.16		9.83 ± 2.84			
Median	9.0		9.50			
Sex	No.	%	No.	%		
Male	18	60.0	20	66.7	χ^2=0.287	0.592
Female	12	40.0	10	33.3		
Cough (After exercise)	No.	%	No.	%		
Yes	6	20.0	23	76.7	**χ2=19.288***	**<0.001***
No	24	80.0	7	23.3		
Chest tightness (After exercise)						
Yes	0	0.0	6	20.0	**χ^2=6.667***	**FEp=0.024***
No	30	100.0	24	80.0		
Wheezes (After exercise)						
Yes	0	0.0	9	30.0	**χ^2=10.588***	**FEp=0.002***
No	30	100.0	21	70.0		
PERF(%)						
Before exercise						
Min. – Max.	90.0 – 98.0		90.0 – 97.0		t =0.577	0.566
Mean ± SD.	94.53 ± 1.98		94.20 ± 2.47			
Median	95.0		95.0			
After exercise						
Min. – Max.	85.0 – 94.0		75.0 – 86.0		**t=9.326***	**<0.001***
Mean ± SD.	88.87 ± 2.64		81.23 ± 3.63			
Median	89.50		82.0			
FEV_1(%)						
Before exercise						
Min. – Max.	90.0 – 96.0		90.0 – 96.0		t =0.140	0.889
Mean ± SD.	92.63 ± 1.77		92.57 ± 1.92			
Median	92.0		93.0			
After exercise						
Min. – Max.	79.0 – 93.0		71.0 – 85.0		**t=9.994***	**<0.001***
Mean ± SD.	86.87 ± 2.86		78.63 ± 3.49			
Median	87.0		79.0			
Eosinophilic count						
Min. – Max.	145.0 – 355.0		189.0 – 360.0		**t=3.194***	**0.002***
Mean ± SD.	253.13 ± 60.97		296.43 ± 42.39			
Median	261.50		295.0			

*t: Student t-test, χ^2: Chi square test, FE: Fisher Exact * significant at (p-value < 0.05)*

Serum periostin levels vary among different age groups. Fig. (5). There was statistically significant positive correlation between serum level of periostin and eosinophilic count at time of enrollment, while there were statistically significant negative correlations between serum level of periostin and (PEFR before exercise, PEFR after exercise, FEV_1 before exercise and FEV_1 after exercise) (p-value < 0.05), Table (7).

4. DISCUSSION

Exercise-induced bronchoconstriction (EIB) is an acute phenomenon where the airways narrow as a result of physical exertion. Although EIB is not observed in all cases of asthma, a significant number of asthmatic patients experience exercise-induced respiratory symptoms, as exercise is one of the most common triggers of.

Table 7. Correlation between serum level of periostin and other numerical variables

Serum level of periostin (ng/dl)	Pearson's correlation	
	r	P
PEFR before exercise (%)	**-0.294***	**0.022***
PEFR after exercise (%)	-0.475	**<0.001***
FEV_1 before exercise (%)	-0.287	**0.026***
FEV_1 after exercise (%)	-0.492	**<0.001***
Eosinophilic count (cell/mcl)	0.414	**<0.001***

**Significant at (p-value < 0.05)*

bronchoconstriction in these patients [6]. Periostin plays an important role in allergic inflammation, including asthma [7]

This also was in agreement with studies made by Inoue et al. [10] and Cho et al. [8]. They found that there were no differences between the asthmatic and healthy children as regard to gender [8-10].

On contrast to this finding Johansson et al., (2016) who found no significant difference between EIB positive and negative groups as regard to BMI [11]. Also, on contrast to us, Kimura et al., (2018) reported that females had higher levels of serum periostin when compared with male subjects [12].

In agreement with studies made by Hoshino et al., (2016); Cho et al. [8] who found that there were no differences between the asthmatic and healthy children as regard to BMI [8,13].

Also, Cho et al. [8] revealed that the maximum decrease in FEV_1 after exercise was significantly greater in asthmatics with positive exercise challenge test than in the other asthmatic groups [8]. This finding was in contrast to Han-Ki Park (2014) who reported that pulmonary function parameters (FEV_1) were relatively lower in EIB-positive than in EIB-negative patients, but the differences were not statistically significant [14].

On contrast to this finding Cho et al. [8] revealed that blood eosinophil counts were significantly higher in asthmatics than in healthy controls [8]. The presence of eosinophilia predicts airway responses evoked by exercise in asthmatic patients [15].

In agreement to a study by Cho et al. [8] who found that serum levels of periostin were significantly greater in asthmatic children with positive exercise challenge test than those with negative test and also healthy controls [8]. Also, Lin et al., (2019) and Hoshino et al., (2016) found that serum concentrations of periostin were significantly higher in patients with asthma than in control subjects [13,16].

In contrast to this finding Inoue et al. [10] did not find any difference in serum periostin levels between patients with childhood asthma and control subjects [17].

Our study yielded higher sensitivity and specificity of periostin than results made by Elhady et al., (2017) who found that periostin level >75 (pg/ml) showed high sensitivity (72.22) and high specificity (88.10) for predicting impaired FEV_1 [18]. Also Inoue et al. [10] who reported that periostin level of 117 ng/ml, had a sensitivity and specificity of 75.0% and 59.3%, respectively to identify children with asthma [10].

It is noteworthy that we should be careful in evaluating serum periostin levels in children because normal ranges vary among different age groups [19].

On contrast to our study Song et al. [9] showed that periostin levels in their study subjects aged 6–15 years were no higher than published values for adults and were not significantly associated with age [9]. Cho et al. [8] who reported that there were no significant correlations between serum levels of periostin and age in any group [8].

In agreement to studies made by Cho et al., [8]; Hoshino et al., (2016) and Elhady et al., (2017) who found significant positive correlations between serum periostin levels and blood eosinophilia [8,13,18]. Also, Kimura et al., (2018) found that blood eosinophil counts were significantly positively associated with serum periostin [12].

There were several limitations to the present study: The sample size was small and in all studied patients asthma was well controlled, so the relation between serum periostin levels and poor asthma control could not be studied.

5. CONCLUSION

Serum periostin levels can be considered as a useful biomarker for diagnosis of EIB in asthmatic children specially when lung function test cannot be done However, cautious is required in evaluating serum periostin levels in children because it varies with age.

CONSENT AND ETHICAL APPROVAL

After obtaining permission from institutional ethical committee and an informed consent was taken from parents of all patients at Tanta university hospital.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Kippelen P, Fitch KD, Anderson SD, Bougault V, Boulet LP, Rundell KW, et al. Respiratory health of elite athletes - preventing airway injury: a critical review. British journal of sports medicine. 2012;46:471-6.
2. Rundell KW, Anderson SD, Sue-Chu M, Bougault V, Boulet LP. Air quality and temperature effects on exercise-induced bronchoconstriction. Comprehensive Physiology. 2015;5:579-610.
3. Szefler SJ, Wenzel S, Brown R, Erzurum SC, Fahy JV, Hamilton RG, et al. Asthma outcomes: biomarkers. The Journal of allergy and clinical immunology. 2012;129:9-23.
4. Sidhu SS, Yuan S, Innes AL, Kerr S, Woodruff PG, Hou L, et al. Roles of epithelial cell-derived periostin in TGF-beta activation, collagen production, and collagen gel elasticity in asthma. Proceedings of the National Academy of Sciences of the United States of America. 2010;107:14170-5.
5. Lopez-Guisa JM, Powers C, File D, Cochrane E, Jimenez N, Debley JS. Airway epithelial cells from asthmatic children differentially express proremodeling factors. Journal of Allergy Clinical Immunology. 2012;129:990-7.
6. Parsons JP, Hallstrand TS, Mastronarde JG, Kaminsky DA, Rundell KW, Hull JH, et al. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. American journal of respiratory and critical care medicine. 2013;187:1016-27.
7. Izuhara K, Conway SJ, Moore BB, Matsumoto H, Holweg CT, Matthews JG, et al. Roles of Periostin in Respiratory Disorders. American journal of respiratory and critical care medicine. 2016;193:949-56.
8. Cho JH, Kim K, Yoon JW, Choi SH, Sheen YH, Han M, et al. Serum levels of periostin and exercise-induced bronchoconstriction in asthmatic children. World Allergy Organ J. 2019;12(1):100-4.
9. Song JS, You JS, Jeong SI, Yang S, Hwang IT, Im YG, et al. Serum periostin levels correlate with airway hyper-responsiveness to methacholine and mannitol in children with asthma. Allergy. 2015;70:674-81.
10. Inoue T, Akashi K, Watanabe M, Ikeda Y, Ashizuka S, Motoki T, et al. Periostin as a biomarker for the diagnosis of pediatric asthma. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2016;27:521-6.
11. Johansson MW, Evans MD, Crisafi GM, Holweg CT, Matthews JG, Jarjour NN. Serum periostin is associated with type 2 immunity in severe asthma. Journal of Allergy Clinical Immunology. 2016;137:1904-7.
12. Kimura H, Konno S, Makita H, Taniguchi N, Kimura H, Goudarzi H, et al. Serum periostin is associated with body mass index and allergic rhinitis in healthy and asthmatic subjects. Allergology international : official journal of the Japanese Society of Allergology. 2018;67:357-63.
13. Hoshino M, Ohtawa J, Akitsu K. Effect of treatment with inhaled corticosteroid on serum periostin levels in asthma. Respirology (Carlton, Vic). 2018;21:297-303.
14. Park HK, Jung JW, Cho SH, Min KU, Kang HR. What makes a difference in exercise-induced bronchoconstriction: an 8 year retrospective analysis. PloS one. 2014;9:871-5.
15. Koh YI, Choi S. Blood eosinophil counts for the prediction of the severity of exercise-

induced bronchospasm in asthma. Respiratory medicine. 2002;96:120-5.
16. Lin LL, Huang SJ, Ou LS, Yao TC, Tsao KC, Yeh KW, et al. Exercise-induced bronchoconstriction in children with asthma: an observational cohort study. Journal of Microbiology, Immunology Infection. 2019;52:471-9.
17. Inoue Y, Izuhara K, Ohta S, Ono J, Shimojo N. No increase in the serum periostin level is detected in elementary school-age children with allergic diseases. Allergology International. 2015;64:289-90.
18. Elhady M. Serum Periostin Level in Children with Bronchial Asthma: A Comparative Study. Journal of Medical Science And clinical Research. 2017;05:15536-42.
19. Nagasaki T, Matsumoto H, Kanemitsu Y, Izuhara K, Tohda Y, Kita H, et al. Integrating longitudinal information on pulmonary function and inflammation using asthma phenotypes. The Journal of allergy and clinical immunology. 2014;133:1474-7, 7.e1-2.

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