Serum periostin levels are associated with asthma severity in children

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Abstract

Background: Periostin has emerged as a novel biomarker in the pathogenesis of T helper 2-type allergic diseases in the last years. The aim of this study was to investigate the association of serum periostin levels with clinical features in children with asthma. Methods: Children with physician-diagnosed asthma who attended regularly to an outpatient pediatric allergy and asthma center were enrolled in the study along with control subjects. Asthma severity and control status of the patients were evaluated according to recent GINA guidelines. Results: A total of 158 children (125 with asthma and 33 age and sex-matched control subjects) with a median age of 10.2 years (range 5.9-17.0) were enrolled. Asthma severity was mild in 41 (32.8%), moderate in 63 (50.4%) and severe in 21 (16.8%) children. Children with asthma had significantly higher periostin levels than controls (53.1 $\pm$ 13.1 vs 43.0 $\pm$ 11.2 ng/mL; $p < 0.001$). The mean serum periostin levels of children with severe asthma (63.8 $\pm$ 10.8) were significantly higher than in children with moderate asthma (53.3 $\pm$ 12.7) and mild asthma (47.4 $\pm$ 11.1) ($p < 0.001$). Serum periostin levels were found to be significantly correlated with asthma severity (Spearman's rho [r]=0.41, $p < 0.001$). Results of multivariable logistic regression analysis demonstrated an association between serum periostin levels and asthma severity in children (OR, 1.10; 95% CI, 1.04-1.15; $p < 0.001$) Conclusion: Serum periostin levels may serve clinicians in identifying children with severe asthma.

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ABSTRACT

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Results: A total of 158 children (125 with asthma and 33 age and sex-matched control subjects) with a median age of 10.2 years (range 5.9-17.0) were enrolled. Asthma severity was mild in 41 (32.8%), moderate in 63 (50.4%) and severe in 21 (16.8%) children. Children with asthma had significantly higher periostin levels than controls (53.1 $\pm$ 13.1 vs 43.0 $\pm$ 11.2 ng/mL; $p < 0.001$). The mean serum periostin levels of children with severe asthma (63.8 $\pm$ 10.8) were significantly higher than in children with moderate asthma (53.3 $\pm$ 12.7) and mild asthma (47.4 $\pm$ 11.1) ($p < 0.001$). Serum periostin levels were found to be significantly correlated with asthma severity (Spearman's rho [r]=0.41, $p < 0.001$). Results of multivariable logistic regression analysis

demonstrated an association between serum periostin levels and asthma severity in children (OR, 1.10; 95% CI, 1.04-1.15; p <0.001)

Conclusion: Serum periostin levels may serve clinicians in identifying children with severe asthma.

Keywords: asthma, biomarker, children, periostin, severe asthma.

Key messages: Periostin, which has emerged as a novel biomarker in the pathogenesis of T helper 2-type allergic diseases in the last years, may serve clinicians in the diagnosis and follow-up of children with severe asthma.

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INTRODUCTION

Asthma is one of the most common chronic diseases of childhood and type-2 airway inflammation is the major feature of the disease. The emergence of biomarkers associated with the underlying airway inflammation is an active research area in adults and children. Up to date, only a limited number of biomarkers have been routinely used in daily clinical practice in patients with asthma and there is still a need for a reliable biomarker not only for the prediction, diagnosis or follow-up of asthma, but also as a candidate target for the treatment options in the future (1).

Periostin is an extracellular matrix protein expressed in fibroblasts and airway epithelial cells and has emerged as a novel biomarker in the pathogenesis of T helper 2-type allergic diseases in the last years. Its role in the diagnosis and treatment of asthma has been highlighted in several adult studies. However, there are limited studies with inconclusive data about the clinical utility of periostin in children with asthma (2).

The aim of this study was to investigate the association of serum periostin levels with several clinical features in children with asthma.

METHODS

Study design, setting and participants

Children aged 6 to 17 with physician-diagnosed asthma who were regularly followed up in the Pediatric Allergy and Asthma Unit of Gulhane School of Medicine between 2014 and 2017 were enrolled in the study along with age and sex-matched control subjects without any physician diagnosed asthma who admitted to outpatient department of our unit for routine medical checkup. They had no history of wheezing or infection during the last 4 weeks before the study enrollment.

Asthma was defined as current symptoms (wheeze and cough) and positive bronchodilator responsiveness (improvement of FEV_1 by 12% or more following administration of 200 mcg salbutamol), and/or a positive response to a trial of therapy with inhaled or oral corticosteroids (3). Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations in the last year according to GINA guidelines. "Mild asthma" is asthma that is well controlled with Step 1 or Step 2 treatment, "moderate asthma" is asthma that is well controlled with Step 3 treatment and "severe asthma" is asthma that requires Step 4 or 5 treatment. Asthma control status of the patients were also evaluated according to GINA guidelines (3). Patients with an acute exacerbation of asthma requiring systemic corticosteroids during the previous 3 months and other known systemic disorders were excluded.

The study was approved by the institutional review board of Gulhane School of Medicine and written informed consent was obtained from parents.

Study measurements

Skin tests

All children underwent skin prick testing (SPT) to common aeroallergens for our region (4), including house-dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), grass pollen mix (Phleum

pratense, Poa pratensis, Dactylis glomerata, Lolium perenne, Festuca pratensis, and Avena eliator) weed pollen mix (Artemisia, Urtica, Taraxacum, Plantago) tree pollen mix (Alnus glutinosa, Corylus avellane, Populus alba, Ulmus minor, Betula alba) molds (Alternaria, Cladosporium, Penicillium, and Aspergillus) and animal dander (cat and dog). Histamine (10 mg/ml of histamine phosphate) and 0.9% saline were used as positive and negative controls, respectively. Weal 3 mm greater than negative control was considered a positive reaction.

Anthropometric measures

Children were weighed wearing minimal clothes and without shoes, Height was rounded to the nearest 0.1 cm and weight was rounded to the nearest 0.1 kg. Subsequently, BMI (Body mass index) was calculated as weight (kilograms) divided by height (meters) squared. BMI z-scores of participants were also calculated (5).

Blood eosinophil counts and serum total IgE levels

Blood eosinophil counts were determined from Coulter Counter (Beckman Coulter, Fullerton, CA, USA) leucocyte measurements. Total serum IgE level was measured using ImmunoCAP (Phadia AB, Uppsala, Sweden).

Serum periostin levels

Measurement of serum periostin levels were made with an enzyme-linked immunosorbent assay (ELISA) at Shino-Test (Kanagawa, Japan), as described previously (6).

Pulmonary function tests

Pulmonary function tests were performed using Zan 100 spirometer (Nspire Health, Oberthulba, Germany) according to recommendations by the European Respiratory Society (7). FEV_1, FEV_1/FVC, and FEF_{25-75} were recorded (8).

Statistical Analysis

Analyses were performed using SPSS Statistics v21.0 (IBM, Chicago, IL, USA). Normally-distributed continuous data were expressed as mean and standard deviation, and not-normally distributed continuous data as median and interquartile ranges (IQR). Group comparisons were carried out using student´s t-test, Mann–Whitney U-test or ANOVA as appropriate for the continuous, and the chi-square test or Fisher test for categorical variables. The correlation coefficients between serum periostin level and other clinical variables were determined using Spearman‘s rank correlation coefficient. Association of severe asthma classes with clinical variables was examined using regression models adjusted for potential confounders, including age, aeroallergen sensitization, BMI z-score, blood eosinophil count and serum periostin level. The odds ratio (OR) and 95% confidence interval (CI) were reported. The diagnostic performances of serum periostin levels to identify children with severe asthma were determined by receiver operating characteristic (ROC) curve analysis. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the selected cut-off point. A P level <0.05 was considered significant.

RESULTS

Descriptive statistics

A total of 158 children (125 with asthma and 33 age and sex-matched control subjects) with a median age of 10.2 years (range 6.0-17.0) were enrolled. Characteristics of the study groups are presented in Table 1. There were no significant differences between the children with asthma and control groups in terms of age, sex, body mass index and total IgE levels. The prevalence of aeroallergen sensitization was significantly higher in children with asthma and they had significantly higher blood eosinophil counts. Children with asthma had significantly higher periostin levels than controls (53.1 ± 13.1 vs 43.0 ± 11.2 ng/mL; $p < 0.001$) (Figure 1a).

Clinical features of children with asthma

Clinical characteristics of the children with asthma are presented in Table 2. Of these 125 children with asthma, 41 (32.8%) had mild, 63 (50.4%) had moderate and 21 (16.8%) had severe asthma. Asthma was controlled in 58.4% of the patients. 69 children (55.2%) were under regular asthma controller treatment and 52 children (41.8%) had an asthma exacerbation in the last year. 87 children (69.6%) had an aeroallergen sensitization.

Correlation between serum periostin levels and clinical variables related to asthma

Serum periostin levels were found to be significantly correlated with asthma severity (Spearman's rho [r]=0.41, $p < 0.001$) and BMI z score (r= -0.31, $p < 0.001$), whereas no correlations were found with age, disease duration, accompanying atopic diseases such as allergic rhinitis and atopic dermatitis, asthma control status, total IgE levels, blood eosinophil counts and lung function parameters (Table 3).

Serum periostin levels and asthma

The mean serum periostin levels of children with severe asthma (63.8 ± 10.8) were significantly higher than in children with moderate asthma (53.3 ± 12.7) and mild asthma (47.4 ± 11.1) ($p < 0.001$) (Figure 1b). No significant differences in serum periostin levels were found in children with asthma when compared according to gender, asthma control status, aeroallergen sensitization, presences of allergic rhinitis or atopic dermatitis (Table 4).

Multivariable regression and ROC analyses for severe asthma

Results of multivariable logistic regression analysis revealed that serum periostin levels were associated with severe asthma in children (OR, 1.10; 95% CI, 1.04-1.15; P <0.001) (Table 5).

Analysis using ROC curves identified the role of serum periostin levels in determining children with severe asthma (AUC: 0.77, 95% CI: 0.67–0.87, $P < 0.001$]. When analysed for the best cut-off value with the highest combined sensitivity and specificity, a cut-off value of 52 ng/ml for serum periostin level was obtained with sensitivity, specificity, PPV, and NPV of 100%, 50%, 29%, and 100%, respectively.

DISCUSSION

In this cross-sectional study, we found that serum periostin levels were significantly higher in children with asthma when compared to healthy controls. Our results also found out an association between serum periostin levels and asthma severity independent from the confounding factors such as BMI and accompanying allergic diseases.

Periostin levels and asthma

Results of several previous childhood studies have demonstrated an association between serum periostin levels and asthma. Song et al. (9) have found that serum periostin levels were higher in children with asthma and associated with airway hyperreactivity. Inoue et al (10). have also found significantly higher serum periostin levels in children with asthma compared to children without any allergic disease in their cross-sectional study and they indicated the possible role of serum periostin in the diagnosis of childhood asthma. On the other hand, Inoue et al. (11) did not detect any increase in serum periostin levels in school age children with allergic diseases including asthma in comparison to healthy children. The serum periostin levels were found to be significantly higher in children than those in healthy adults. They have speculated that the high baseline levels of serum periostin due to increased bone metabolism in childhood might have masked the possible further increase due to allergic diseases. In our study serum periostin levels were higher in children particularly with moderate and severe asthma.

Predictive role of periostin for asthma

Several attempts were made to investigate the role of periostin to predict the development of asthma in the future. Anderson at al.(12) have prospectively followed up the children from COAST (Childhood Origins of ASThma Study) cohort and longitudinally investigated the role of several biomarkers of type 2 inflammation such as aeroallergen sensitization, blood eosinophils and serum periostin levels in the development of

asthma during the childhood period. They have found that, along with other variables, high serum periostin levels at the age of 2 years is a risk factor for asthma by school-age. However, they have also addressed a concern regarding the possible confounder effect of the linear growth on serum periostin levels during the early-childhood phase. Castro-Rodriguez et al.(13) have performed a case-control study in preschoolers with recurrent wheezing episodes and compared periostin levels according to their asthma predictive index result. No significant difference was found in periostin levels between children with positive and negative asthma predictive index. Recently, Guvenir et al.(14) investigated the role of periostin in young children with wheezing episodes for the prediction of asthma development. However, their results did not reveal periostin as a predictive factor for future asthma in young children, either.

Association between asthma control and periostin

There are conflicting results about the relationship between serum periostin levels and asthma control status in children. El Basha et al.(15) have found significantly higher serum periostin levels in children during an asthma exacerbation compared to children with stable asthma and healthy controls whereas In contrast to these findings Mena et al. (16) have found an inverse association with lower serum periostin levels in children with uncontrolled asthma. Licari et al. (17) did not find an association between asthma control and serum periostin levels in 121 children with allergic asthma. In our study serum periostin was not associated with asthma control, either. Asthma control status is determined according to the symptoms in the last 4 weeks and it can be different in every clinical visit. However, asthma severity is based on the step of medications to control asthma symptoms in the last year and it can be a better instrument in search of a biomarker that reflects the degree of inflammation in a chronic disease like asthma.

Association between asthma severity and periostin

There are also inconsistent results from the studies which investigated the association between asthma severity and serum periostin levels. The results of Licari et al.(17) and Konradsen et al. (18) did not reveal an association between asthma severity and serum periostin levels. On the other hand, Song et al. (9) have explored the relationship between periostin and airway hyperresponsiveness (AHR) in children with asthma and found a significant correlation between the degree of AHR and periostin levels. Similarly, Cho et al. (19) found significantly higher periostin levels in children with positive exercise and mannitol tests when compared to children with asthma and negative results. Recently, the findings of Knihtilä et al.(20) have demonstrated a significant correlation between serum periostin levels, airway-hyperreactivity and bronchodilator responsiveness in 49 children with asthmatic symptoms. In our study we found a significant and independent correlation between asthma severity and serum periostin levels. A serum periostin value of 52 ng/ml was emerged as the best cut-off level to differentiate children with severe asthma with high sensitivity and negative predictive values, whereas the specificity and positive predictive value for this cut-off were not satisfactory. According to our findings, it can be postulated that low serum periostin levels may serve clinicians better in excluding severe asthma in children.

Body mass index and serum periostin

In according with the previous adulthood studies (21, 22), we found a negative correlation between serum periostin levels and body mass index in children with asthma along with healthy controls. In our previous studies, we have demonstrated associations between anthropometric measures and asthma severity along with pulmonary functions (23-25). In the current study, our results did not reveal an independent association between body mass index and asthma severity. The different study design and the lack of controls group with obese children is the most plausible explanation. Addition of serum periostin measurement into the studies can help us to better understand the interaction between obesity and asthma in the future.

Limitations and strengths

There are several limitations in the present study. First, the diagnostic performance of serum periostin in identifying children with severe asthma were relatively low. It seems that further studies including more children particularly with severe asthma can help to determine different cut-off values with better stati-

stical performances. Furthermore, periostin is a bone-derived extracellular matrix protein that is secreted by osteoblasts and in growing children the indicative role of periostin related to the airway inflammation and consequently asthma severity may be affected due to the fast-linear growth in school-age children. On the other hand, it was performed in a center which was specialized for children with asthma and allergic diseases. The diagnostic procedures and the longitudinal follow-up of the patients were made by pediatric allergy and asthma specialists conforming with the international standard GINA guidelines. Its controlled design with the inclusion of patients with different severity grades who were under regular follow-up enabled us to demonstrate the possible interactions between features related to childhood asthma and periostin.

Conclusion

In conclusion, we demonstrated a significant and independent association between serum periostin and asthma severity in children. Our findings highlight the diagnostic role of periostin in identifying children with severe asthma. Further studies are needed to better demonstrate the role of periostin in the asthma pathogenesis and clinical utility for the physicians dealing with children with asthma.

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Table 1. Demographic and laboratory characteristics of the study groups (n=158)

	Asthma (n=125)	Control (n=33)	p-value
Age (years)	10.2 (7.8-12.7)	11.4 (7.5-13.9)	0.53
Male sex, (%)	75.2	66.7	0.32
BMI (kg/m^2)	19.8 ± 4.1	19.4 ± 4.1	0.72
BMI z-score	0.45 ± 1.25	0.44 ± 1.08	0.97
Aeroallergen sensitization, (%)	69.6	18.2	< 0.001
Serum periostin (ng/mL)	53.1 ± 13.0	43.3 ± 11.2	< 0.001
Eosinophils, %	3.4 (2.1-5.6)	2.1 (1.4-3.9)	0.007
Eosinophils, (/ml)	255 (150-428)	120 (80-230)	< 0.001
Total IgE (IU/ml)	71 (20-167)	27 (11-138)	0.12

Abbreviations: BMI, body mass index. Data are presented as percentage, median (interquartile range) or mean ± standard deviation	Abbreviations: BMI, body mass index. Data are presented as percentage, median (interquartile range) or mean ± standard deviation	Abbreviations: BMI, body mass index. Data are presented as percentage, median (interquartile range) or mean ± standard deviation	Abbreviations: BMI, body mass index. Data are presented as percentage, median (interquartile range) or mean ± standard deviation

Table 2. Clinical characteristics of the children with asthma (n=125)

Age at symptoms start (years)	4.5 (2.0-7.0)
Age at the diagnosis (years)	6.3 (4.8-9.8)
Disease duration (years)	5.1 (2.4-7.9)
Allergic rhinitis	61.6
Atopic dermatitis	13.6
Asthma controller therapy	55.2
Asthma exacerbation in last year	41.6
Asthma severity - mild - moderate - severe	32.8 50.4 16.8
Asthma control level - controlled - partially controlled - uncontrolled	58.4 20.8 20.8
Aeroallergen sensitization	
- Grass pollens	57.6
- House dust mites	18.4
- Cat dander	11.2
- Mold	8.0
- Dog dander	6.4
- Tree pollens	4.0
- Weed pollens	3.2
Data are presented as percentage or median (interquartile range)	Data are presented as percentage or median (interqu

Table 3. Spearman's correlation coefficients between serum periostin level and other clinical variables in children with asthma

Age, years	
Disease duration, years	
Asthma severity	
Asthma control status	
Atopic dermatitis	
Allergic rhinitis	
BMI, z-score	
Total IgE (IU/mL)	
Eosinophils, (%)	
Eosinophils, (/ml)	
FEV_1, pred %	
FEV_1/FVC ratio	
FEF_{25-75}, pred %	
Abbreviations: BMI, body mass index; FEF_{25-75}, forced expiratory flow between 25% and 75%; FEV_1, forced expiratory vo	

Table 4. Comparison of serum periostin levels according to clinical variables in children with asthma

	Serum periostin (ng/ml)	p-value
Gender -boys -girls	53.8 ± 13.5 51.3 ± 11.6	0.36
Asthma severity -mild -moderate -severe	47.4 ± 11.1 53.3 ± 12.7 63.8 ± 10.8	<.001
Asthma control status -controlled -partially controlled -uncontrolled	52.9 ± 13.4 56.7 ± 12.1 50.1 ± 12.4	0.18
Aeroallergen sensitization -yes -no	54.3 ± 12.9 50.4 ± 12.9	0.13
Atopic dermatitis -yes -no	55.7 ± 12.5 52.7 ± 13.1	0.38
Allergic rhinitis -yes -no	53.6 ± 12.4 52.4 ± 14.1	0.61
Data are presented as mean ± standard deviation	Data are presented as mean ± standard deviation	Data are presented as mean ± standard deviation

Table 5. Multivariable logistic regression analysis for severe asthma

Variable	OR (95% CI)
Age	1.11 (0.91-1.34)
Aeroallergen sensitization	0.44 (0.15-1.32)
BMI, z-score	1.01 (0.65-1.58)
Eosinophils (/ml)	1.01 (0.99-1.01)
Serum periostin level	1.10 (1.04-1.15)
Abbreviations: BMI: Body mass index; CI, confidence interval; OR, odds ratio	Abbreviations: BMI: Body mass index; CI

Figure Legends

Figure 1. Comparison of serum periostin levels in study groups

1a. Asthma vs Healthy controls

1b. Asthma group according to severity

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`Figure 1.pptx` available at https://authorea.com/users/381831/articles/497732-serum-periostin-levels-are-associated-with-asthma-severity-in-children