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Periostin concentration in exhaled breath condensate in children with mild asthma

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ABSTRACT

Objective: Periostin is considered to be a marker of eosinophilic inflammation in patients with asthma. However, there are no literature data on exhaled breath condensate (EBC) periostin level in pediatric patients with asthma. The aim of this study was to analyze EBC periostin concentration in children with mild asthma and to evaluate the potential usefulness of EBC periostin level as a biomarker for the disease.

Methods: EBC and serum periostin concentrations were measured by enzyme-linked immunosorbent assay in 23 children with asthma and 23 healthy controls.

Results: EBC periostin concentration was 250- to 780-fold lower than that found in serum. No significant differences between serum nor EBC periostin concentration in asthmatics and the control group were showed. The comparison between children with Th2 and non-Th2 type of asthma did not show significant differences in periostin concentration, both in serum and EBC. Serum periostin concentration inversely correlated with BMI and age not only in asthma patients but also in controls.

Conclusions: In children with mild asthma, periostin may be measured not only in serum but also in EBC. The low periostin level in patients with mild asthma and lack of difference between asthmatic subjects and controls indicate that EBC periostin may not be useful as an asthma biomarker in this group.

Abbreviations: AHR: airway hyperresponsiveness; ATS: American Thoracic Society; BMI: body mass index; EBC: exhaled breath condensate; ERS: European Respiratory Society; FeNO: fractional exhaled nitric oxide; FEV₁: forced expiratory volume at first second; FVC: forced vital capacity; GINA: Global Initiative for Asthma; GLI: Global Lung Initiative; ICS: inhaled corticosteroids; sIgE: specific IgE; SCS: systemic corticosteroids.

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Introduction

Asthma is one of the most common chronic respiratory diseases in children. Currently, it affects approximately 15% of school-aged children in Europe but its incidence and prevalence are still increasing (1). Asthma is a highly heterogeneous disease, with the clinical presentation and response to treatment strongly related to certain clinical, inflammatory, and molecular features (2). These features form the basis to define different asthma phenotypes (3). Several biomarkers have been found to be important tools in asthma phenotyping. Some of these biomarkers can be assessed only at the local level [e.g. fractional exhaled nitric oxide, FeNO (4)],

while the other can be measured both at the local and systemic levels [e.g. sputum eosinophils (5) and blood eosinophils (6)]. It can be supposed that the biomarker level in airway samples might be a more reliable measure of local inflammatory process than systemic biomarker concentration. This is because a serum biomarker level is usually affected by a variety of factors, including different sources, and routes and rate of elimination (7). Thus, it may not reflect the local airway phenomena. One of the recently studied and promising biomarkers of Th2 inflammation in asthma is periostin (8,9).

Periostin is a matrix protein, expressed in fibroblasts and epithelial cells, involved in various biological processes such as cell proliferation, cell invasion, and

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angiogenesis (8,10,11). It is associated with eosinophil migration and tissue infiltration (12). Periostin has been found to support chronic allergic inflammation in response to Th2 cytokines and to be upregulated in bronchial epithelial cells by IL-4 and IL-13 stimulation (11,13). Several *in vitro* and *in vivo* studies have suggested that periostin is associated with the severity of asthma and may play a potential role in the diagnosis of asthma in adults and children (14,15). It should be emphasized, however, that serum periostin is not specific for asthma and participates in the pathophysiology of numerous other diseases, including allergic rhinitis and chronic rhinosinusitis (16,17).

Studies on serum periostin in children showed significantly higher values in severe asthma compared with healthy controls (9,18). Several studies reported correlations between serum periostin and airway hyperresponsiveness (AHR), blood eosinophil count, and FeNO in asthmatic children (9,19). However, when interpreting serum levels of periostin in children, it should be remembered that this protein is also secreted by osteoblasts (20). Therefore, serum periostin is of limited usefulness in the investigation of inflammatory diseases during typical bone turnover of the pediatric age. As sputum induction cannot be sufficiently performed in children younger than 6 years [sputum induction in children aged >6 years is safe and has a satisfactory success rate (21)], the only samples from the lower airways that can be obtained using noninvasive methods are exhaled breath and exhaled breath condensate (EBC). Airway inflammation leads to increase of exhaled nitric oxide (eNO), which is a recognized marker of eosinophilic airway inflammation (22,23).

EBC analysis is increasingly applied in studies on airway diseases in both the adult and pediatric population (24). Although numerous biomolecules, markers of airway inflammation, and oxidative stress have been identified and measured in the EBC of children with asthma (24), to our knowledge, there have been no studies on EBC periostin concentration. The majority of periostin studies in children were focused on periostin measurements in serum, and importantly, included mainly children with severe asthma receiving anti-inflammatory treatment (18,25). In fact, data on EBC periostin concentration in adult asthmatics are also scarce (26). Therefore, we undertook a study to determine periostin concentration in EBC in children with mild asthma, as well as to evaluate the potential usefulness of EBC periostin level as a biomarker for the disease. The specific aims of the study were: (1) to assess the feasibility of EBC periostin measurements,

(2) to compare EBC periostin level in children with asthma and healthy controls, (3) to compare periostin concentration in EBC and serum, (4) to search for correlations between EBC periostin and other biomarkers of asthma, and, finally, (5) to compare EBC periostin in children with Th2- and non-Th2 asthma.

Material and methods

Study design and participants

This cross-sectional, prospective study involved 23 children with mild allergic asthma and 23 controls. All participants were recruited from the Department of Pediatric Pneumonology and Allergy, Medical University of Warsaw between 2015 and 2017. A two-step recruitment process was applied. The first step comprised a routine visit in the outpatient clinic during which previous results (including peripheral blood eosinophils) were evaluated, the diagnosis of asthma was confirmed, and the patients expressed their willingness to participate in the study. The second step comprised a second visit scheduled specifically to explain the study details and to obtain a written consent and to obtain samples for the proper analysis. Only children with asthma in whom treatment with steroids had not yet been initiated or was ceased due to reasons not related to the study were included. Asthma was diagnosed according to the 2015 Global Initiative for Asthma guidelines (GINA) (27). The inclusion criteria for this group were: (1) no treatment with systemic or inhaled corticosteroids (SCS or ICS) and (2) lack of exacerbation for at least 6 weeks prior to enrollment.

The control group was recruited from patients referred to outpatient surgery clinic for minor plastic surgery (e.g. excision of cutaneous nevi). This included healthy children with no history of atopy or any respiratory symptoms, matched to the study patients in terms of age and sex. The major exclusion criterion for both groups was acute respiratory infection within 6 weeks prior to inclusion to the study.

Comprehensive medical history with special attention to data on the onset of asthma symptoms, duration of the disease, severity of asthma, and history of atopy were collected from all subjects. All participants underwent lung function tests, FeNO measurement, blood sampling for basic laboratory investigations (including blood eosinophils, C-reactive protein, total and specific IgE) and periostin concentration, and EBC collection for the measurement of periostin level. All the procedures were performed on the same day.

The study was approved by the Bioethics Committee of the Medical University of Warsaw (permission No. 26/2015). Written informed consent was obtained from the parents or guardians of all participants following a detailed explanation of the principles of the study.

Pulmonary function and assessment of atopic/inflammatory status

Spirometry (Vyntus IOS spirometer CareFusion, San Diego, CA, USA) was performed according to the European Respiratory Society/American Thoracic Society (ERS/ATS) recommendations (28,29). Pulmonary function parameters were calculated using Global Lung Initiative (GLI-2012) reference equations and presented as the median (IQR) values of z-scores (30).

Atopic status was assessed by total serum IgE and the presence of specific IgE against common aeroallergens by using the UniCAP automatic analyzer (ImmunoCAP System, Phadia AB, Uppsala, Sweden). A concentration >0.35 kU/L for at least one allergen was considered positive. Sensitization for the following 22 common allergens were tested: house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), *Aspergillus fumigatus*, *Cladosporium* spp., *Penicillium notatum*, *Alternaria ascomycota*, sweet vernal grass, cock's-foot, common ragweed, timothy-grass, rye, wormwood, ribwort plantain, birch, gray alder, hazel, oak, dog, cat, horse, hamster, anti-CCD.

Exhaled nitric oxide (FeNO) was measured using an online device at a constant flow of 50 ml/s (NOA 280i Sievers, CO, USA) according to the ATS and the ERS recommendations for children (31).

Blood analysis was performed for eosinophil count.

For an additional analysis, we divided asthma children according to blood eosinophil count and FeNO level into two groups: Th2 asthma [blood eosinophil count $\geq 400 \times 10^9/L$ (32) as previously documented and in the measurement performed during the study and FeNO ≥ 35 ppb (33,34)] and non-Th2 asthma (blood eosinophil count $< 400 \times 10^9/L$ and FeNO < 35 ppb).

Exhaled breath condensate collection

EBC samples were collected using ECO screen Jaeger (Höchberg, Germany) according to the manufacturer's instructions and the ERS/ATS recommendations (35). The samples were obtained during tidal breathing (10 min) through a mouthpiece with a saliva trap in sitting position. The respiratory samples were immediately stored at -80°C and kept frozen until analysis.

The collection of EBC was performed before spirometry and after FeNO measurement (26).

Periostin measurement

Periostin concentration was measured in serum and non-concentrated EBC with ELISA method (Periostin/OSF-2 Human ELISA, Phenix Pharmaceuticals, Inc., CA USA). The serum was $10 \times$ diluted for the determination of periostin level. Serum and EBC periostin were measured in duplicate, and the average score from two assay results was used for statistical analysis. The range and the sensitivity of the applied kit were 0.027 – 20 ng/mL and 0.027 ng/mL, respectively.

Statistical analysis

Sample size estimation was based on data from an earlier study by Song et al. (19). To detect the significant difference between studied groups (5 ± 3 ng/mL) with t test with a power of 80% and a significance level of 5% and standard deviation value similar to those reported in the paper by Song et al. (19), the sample size was estimated as 20 asthma patients.

Statistical analysis was performed with Statistica for Windows (StatSoft, Tulsa, OK, USA version 10). p values < 0.05 were accepted as statistically significant. Data were expressed as medians and interquartile ranges (IQRs) (25–75th percentiles) or numbers and percentages. Quantitative data distribution was assessed using Shapiro–Wilk test. Comparisons between the groups were made using nonparametric Mann–Whitney test. To evaluate the significance of correlation coefficient, Spearman correlation test was used. To draw 3 D surface plots, the nonlinear estimation with distance-weighted least squares smoothing procedure was applied.

Results

Patient characteristics

Forty-six children, including 23 asthmatics and 23 healthy controls, were enrolled. Basic demographic and clinical characteristics of the study participants are shown in Table 1. Among asthmatics, 21 patients (91.3%) had rhinitis, 7 (30.4%) had conjunctivitis, and 4 (17.4%) had skin allergy. Asthma patients and healthy subjects differed significantly in terms of total serum IgE, FeNO level, and the number and percentage of peripheral blood eosinophils (Table 1). In patients with asthma, median concentration of specific IgE for 22 allergens was 5.7 (0.18–14.5) U/L.

Table 1. Basic demographic and clinical characteristics of the study groups.

Parameter	Asthma (n = 23)	Controls (n = 23)	p value
Demographic characteristics			
Age (years)	11 (7–14)	12 (7–15)	0.33
Sex (M/F) (n)	12/11	8/15	0.32
BMI (kg/m ²)	19 (16.6–20.8)	18.3 (15.4–19.5)	0.35
Duration of asthma symptoms (months)	36 (12–72)	n/a	–
Pulmonary function			
FEV ₁ (z-score)	−0.27 (−1.56 to 0.4)	−0.11 (−0.67 to 0.9)	0.2
FVC (z-score)	0.15 (−0.65 to 0.7)	−0.16 (−0.72 to 0.6)	0.57
FEV ₁ /FVC (z-score)	−0.54 (−1.5 to 0.2)	0.89 (−0.04 to 1.32)	0.002
Selected laboratory parameters			
FeNO (ppb)	30 (11.4–58.7)	9.8 (6.4–14.9)	0.0002
Total IgE (U/L)	348 (116–780)	42.1 (20–241)	0.006
Blood WBC × 10 ⁹ /L	7.4 (5.5–8.5)	6.9 (5.4–11.1)	0.91
Blood neutrophils × 10 ⁹ /L	3.6 (2.4–4.8)	3.3 (2.7–6)	0.59
Blood eosinophils × 10 ⁹ /L	0.35 (0.13–0.5)	0.1 (0.06–0.3)	0.01
Blood eosinophils %	4.6 (2.2–9.6)	1.4 (1–3.4)	0.006

Note: Data presented as median and IQR where applicable. BMI: body mass index; FEV₁: forced expiratory volume at first second; FVC: forced vital capacity; FeNO: fractional exhaled nitric oxide; n/a: not applicable.

Table 2. Exhaled breath condensate and serum concentration of periostin in children with asthma and controls.

Periostin concentration	Asthma (n = 23)	Control (n = 23)	p value
EBC periostin (ng/mL)	0.04 (0–0.11)	0.1 (0.05–0.15)	0.09
Serum periostin (ng/mL)	31.3 (12.3–45.4)	25.2 (5.3–31.8)	0.34

Note: Data presented as median and IQR. EBC: exhaled breath condensate.

Periostin concentrations

There was no significant difference between EBC periostin concentration in asthmatics and the control group (Table 2). The absolute value of median serum periostin concentration was higher in children with asthma than in controls (31.3 vs. 25.2 ng/mL), but the statistical analysis showed that the difference was not significant. EBC periostin concentration was 250– to 780-fold lower than that found in serum.

The comparison between children with Th2 (n = 5) and non-Th2 (n = 9) type of asthma did not show significant differences in periostin concentration, both in serum and EBC. In the Th2 subgroup, periostin concentration in EBC did not statistically differ (p = 0.69) from the non-Th2 type (0.08 ng/mL vs 0.1 ng/mL), and the same was true for serum (18.3 ng/mL vs 33.9 ng/mL with p = 0.79).

In the group of children with asthma, serum periostin correlated inversely with EBC periostin (r = −0.44, p = 0.04), whereas in the group of healthy children we did not find such a correlation (Figure 1). In asthmatics, a negative correlation was also found between serum periostin and age (r = −0.63, p = 0.001) and BMI (r = −0.53, p = 0.009), but not with serum eosinophil count (r = 0.14, p = 0.5), FeNO (r = −0.29, p = 0.17) and atopy.

Although serum periostin did not correlate with total IgE, we found a negative correlation between serum periostin level and concentration of specific IgE

for certain allergens, including birch pollen, alder pollen, hazel pollen, oak pollen, rye pollen, mugwort pollen, plantain pollen, and *Alternaria*.

In contrast to serum periostin, there was a positive correlation between EBC periostin and atopy (r = 0.5, p = 0.01). We did not find significant correlations between EBC or serum periostin and blood eosinophils, FeNO or IgE level. However, when the pattern of EBC periostin was evaluated in the context of both blood eosinophils and FeNO, the highest EBC periostin levels were observed in children with high FeNO and high eosinophils, combined (Figure 2, panel A). Such a relationship was not demonstrated for serum periostin (Figure 2, panel B).

In controls, similarly to the group of asthmatics, serum periostin correlated inversely with age (r = −0.59, p = 0.003) and BMI (r = −0.53, p = 0.009). We did not find any correlations between EBC periostin and periostin level in serum, pulmonary function, and selected blood laboratory investigations in the control group.

Discussion

The present study was aimed to evaluate the feasibility and usefulness of periostin measurement in EBC in steroid-naïve children with mild asthma. We demonstrated that the measurement of periostin in EBC with ELISA was feasible, but the EBC periostin levels were 250–780-fold lower than those in serum. We did not find a significant difference between EBC periostin concentration in children with asthma and controls. Also, there were no significant differences between EBC, as well as serum periostin level in children with Th2 and non-Th2 asthma. Serum periostin concentration inversely correlated with BMI and age not only in asthma patients but also in controls.

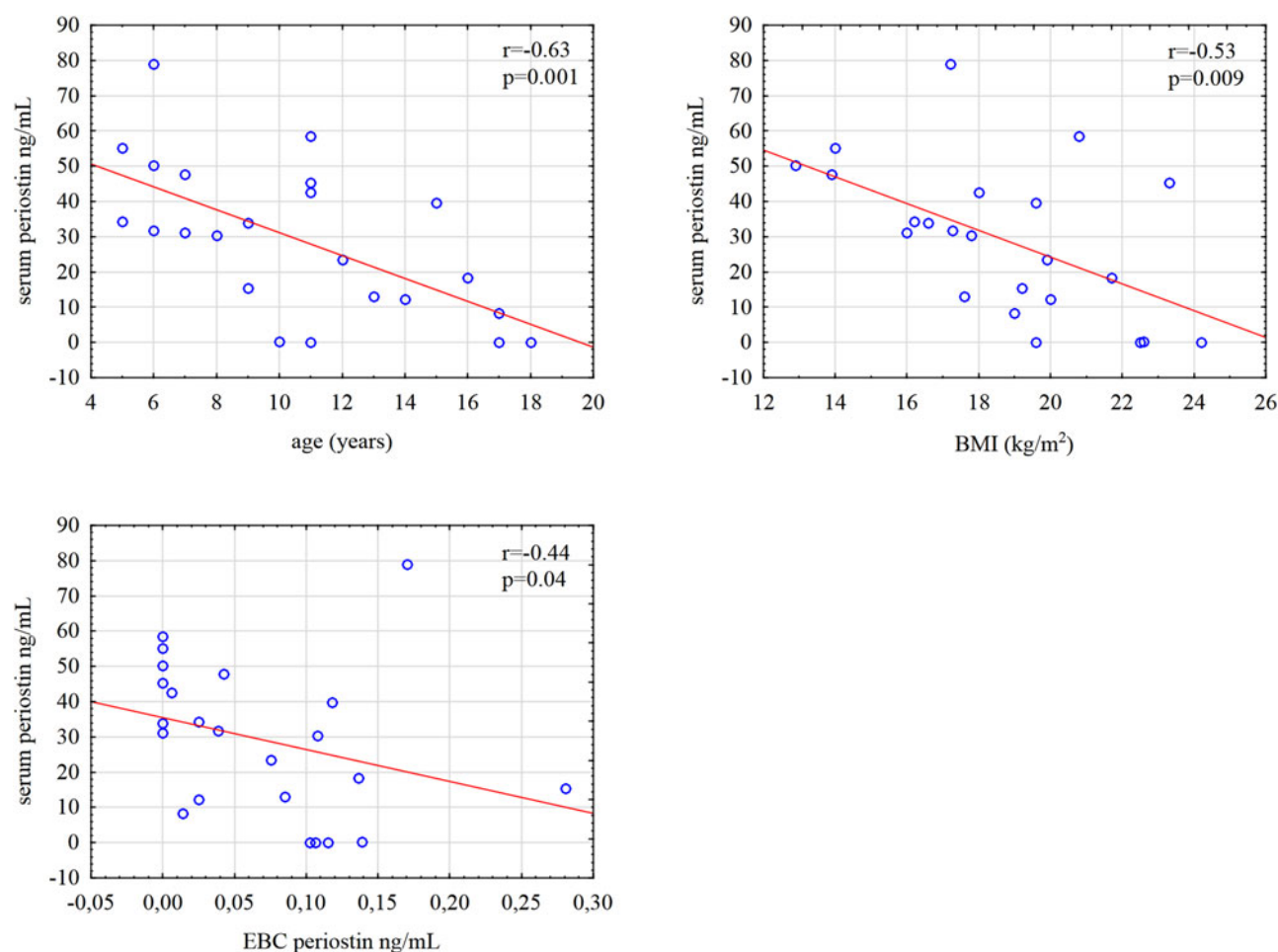


Figure 1. Correlations between serum periostin concentration and selected anthropometric and functional parameters in the group of children with asthma. BMI: body mass index; EBC: exhaled breath condensate.

Searching for novel, easily available asthma biomarkers and use of noninvasive methods of asthma diagnosis, phenotyping and monitoring are particularly important in children. Following the progress in the use of FeNO in the management of asthma, we evaluated the potential usefulness of EBC periostin measurement in childhood asthma diagnosis and phenotyping. It should be emphasized that, to our knowledge, this was the first study assessing the EBC periostin concentration in children with asthma. All earlier publications on EBC periostin referred to adult asthmatics and these studies were in fact the basis for the current study (26,32,36). Our results are consistent with the results presented by Wardzyńska et al. who reported no differences between EBC periostin levels in adult asthmatics and controls (36). On the other hand, opposite results were also reported. In one of our previous studies, we found that EBC periostin concentration was higher in asthma patients compared to controls (26). Similarly, Carpagnano et al. showed that periostin levels were detectable in EBC and in induced sputum (IS) supernatant with significant

differences between adults' patients with severe asthma and patients with mild-to-moderate asthma and controls (32). The above findings may help explain the lack of difference between EBC periostin level in asthmatics and controls in our current study. It might be supposed that more severe asthma and more severe airway inflammation are necessary to reveal the significant difference in EBC periostin levels.

In terms of the lack of correlation between EBC periostin and patients' age, pulmonary function, eosinophil count, or FeNO, our results are similar to those reported by Wardzyńska et al. (36), who found that asthmatics with rhinitis had higher levels of EBC periostin than those without. This may indicate that the type and severity of upper airway inflammation may contribute to EBC periostin level.

Regarding serum periostin level in asthmatics and controls, our findings can be supported by the results presented by other authors. Inoue et al. reported no increase in serum periostin level in children with allergic diseases compared to control subjects (37).

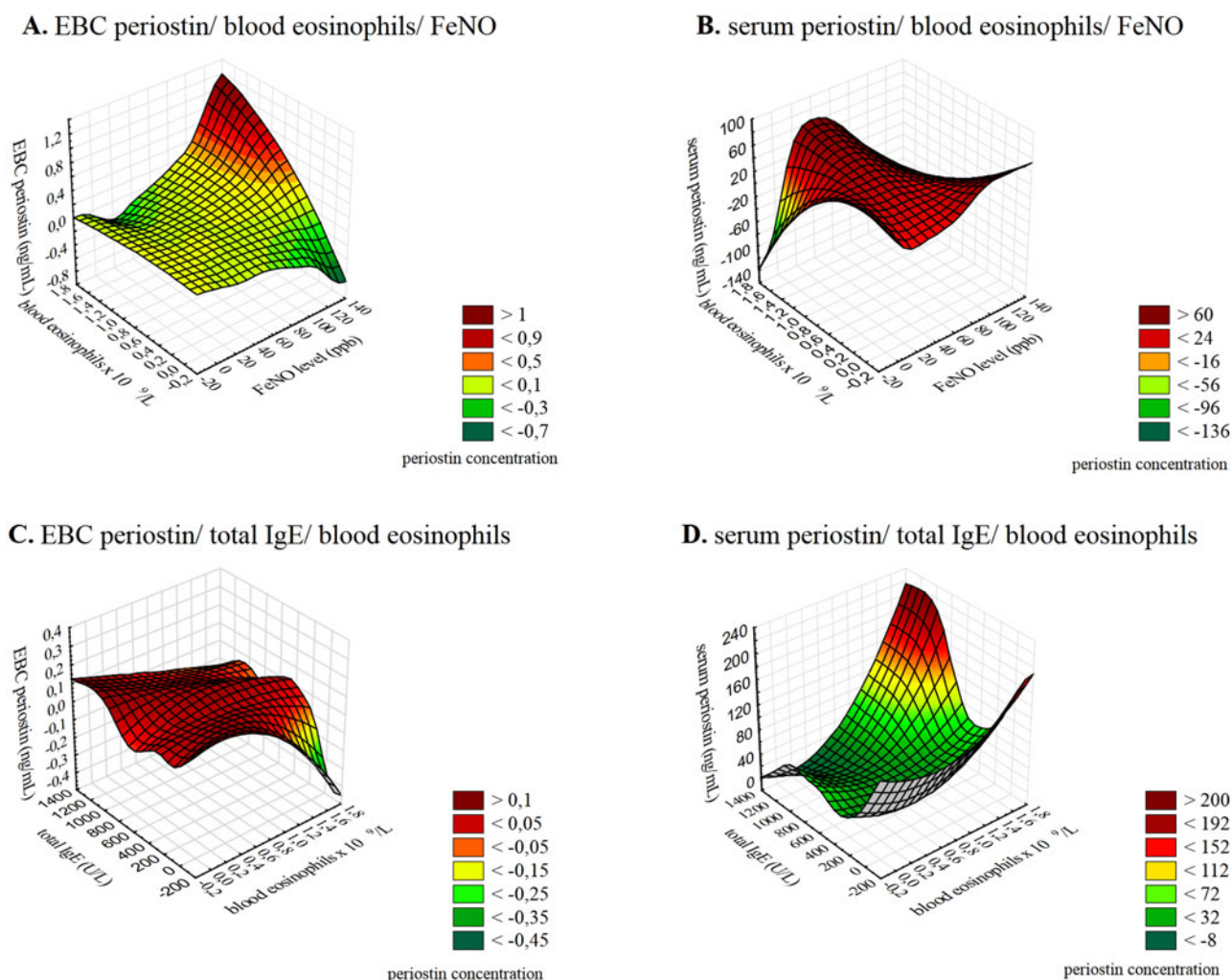


Figure 2. Relationships between EBC/serum periostin concentration and selected laboratory parameters.

Likewise, Castro-Rodriguez et al. did not find any differences between serum periostin level in children with or without positive asthma predictive index (38). However, as for EBC periostin, there were also studies which demonstrated increased level of serum periostin in asthmatics (9,18,19,39). Discrepancies between the results of different studies may be probably attributed to the different degrees of asthma severity in the investigated groups. It may be speculated that the more pronounced and persistent airway inflammation the higher level of serum periostin (32).

Serum periostin levels between 30 and 150 ng/mL in adult asthmatics and between 50 and 134 ng/mL in children with asthma have been reported (8,9,40,41). This level is largely dependent on the severity of the disease and type of ELISA kit used. Data on EBC periostin in asthma patients come from adults only, with the values ranging between 0.75 and 3 ng/mL (32,36). In our patients, both serum and EBC periostin were lower than previously reported. This may probably be attributed to the fact that we studied children (who

are characterized by lower expiratory flows limiting the influx of volatile compounds to exhaled air) with mild asthma (i.e. lower degree of disease severity than in earlier investigated patients).

As already mentioned, serum periostin is a relatively nonspecific biomarker that may be influenced by different factors. In our study, serum periostin level correlated inversely with age in both asthmatics and controls. The same observations came from Inoue et al. (9) and Anderson et al. (39) studies. As periostin is a component of the extracellular matrix and regulates type I collagen formation, which is important for bone, tendon, and skin development, the above relationship is probably associated with bone turnover and growth. Similarly to Kim et al. (40), we also found a significant negative correlation between serum periostin and BMI which may be associated with intensive growth of the body in young children.

Although there have been several articles on the relationship between periostin and type 2 inflammatory response in adult asthma (15,26,41), studies in

children are still scarce (25,42). In our study, the comparison between children with Th2-type and non-Th2 type of asthma did not show significant differences in periostin concentration, both in serum and EBC. This may suggest that in children with mild asthma neither EBC nor serum is an appropriate material to measure periostin level in the context of the type of airway inflammation. The criteria for discriminating Th2 and non-Th2 asthma in our study may seem controversial as it was based on FeNO and blood eosinophil count. On the other hand, due to the age of the investigated patients, sputum induction would have been difficult to accomplish (21). In contrast, blood eosinophil count which is also mentioned as a marker of Th2 asthma (32) was readily available. We did not find significant differences in periostin levels between children with Th2 asthma and those with non-Th2 asthma; however, this could have resulted from the low number of subjects in both groups.

Assuming that in mild asthma one biomarker might be not sufficient to differentiate between patients with different asthma endotypes, including the type of airway inflammation, we performed an additional analysis that included periostin and two other asthma biomarkers. We believe, the results of this analysis are interesting, even though they are expressed only as graphs. If two biomarkers of Th2 inflammation – one systemic (blood eosinophils) and one local (FeNO) – were used, the highest EBC periostin levels were found in those who expressed both a high eosinophil count and a high FeNO. One could speculate that if two local biomarkers of Th2 asthma type (e.g. FeNO and IS eosinophils) could be applied, then the relationship between local indices i.e. EBC periostin concentration, high IS eosinophils number, and high FeNO would be even more pronounced. Unfortunately, as 25% of our children with asthma were below the age of 7 years, IS could not have been easily collected and was not included in the study protocol. In contrast to EBC periostin, there was no clear relationship between serum periostin, blood eosinophils, and FeNO (Figure 2, panel B). It can be supposed that high local FeNO does not affect or only minimally affects serum periostin concentration. Further, when two systemic Th2 biomarkers were used, the highest serum periostin level was demonstrated in patients with high IgE level and high blood eosinophil count. However, that relationship was more ambiguous than that found for EBC periostin, blood eosinophils, and FeNO.

Although EBC is a promising technique in the assessment of lower airway inflammation, some problems

related with its application in research have still not been resolved. These include the lack of a standard procedure to collect exhaled breath samples and a standard procedure of reporting the results of EBC analysis. Recently, Horváth et al. proposed technical norms and recommendations for EBC collection and analysis; however, some issues seem to be still not adequately addressed (35,43). Only small numbers of healthy children were included in studies on EBC analysis as reference groups (24), therefore reference values for the EBC biomarkers in children are not available. In addition, new understanding of EBC formation and improvement in its analysis make the comparison between different studies difficult.

We are aware about several limitations of our study. First, as it involved only children with mild asthma, the results are valid only for this degree of asthma severity and should not be extrapolated for the entire population of asthmatic children. It cannot be excluded, that the inclusion of children with severe asthma would result in more spectacular results in terms of differences between asthmatics and controls. However, as our intention was to measure EBC periostin which was not affected by treatment, we applied the inclusion criterion of mild, non-treated asthma. Second, albeit the number of patients was even slightly higher than estimated prior to the study, it was relatively still small and this could be responsible for an inadequate power to show significant differences between studied groups. Third, as the study included children, the study protocol did not include more invasive studies that could better characterize and quantify airway inflammation (e.g. sputum induction, fiber optic bronchoscopy with bronchial wall biopsy sampling). We may suppose that the assessment of EBC periostin in the context of different measures of local Th2 inflammation would shed more light on the complex relationship between airway inflammation, serum, and EBC periostin. Another limitation of the study are the small Th2 and non-Th2 subgroups of asthma patients, what, most likely, contributed to the lack of statistically significant differences in periostin levels.

Conclusions

In children with mild asthma, periostin may be measured not only in serum but also in EBC. The low periostin level in patients with mild asthma and lack of difference between asthmatic subjects and controls may indicate the limited usefulness of EBC periostin as an asthma biomarker in this specific group.

Declaration of interest

No conflict of interest exists for all authors.

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