



# Serum periostin level is not associated with allergic rhinitis or allergic sensitization in Korean children



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## ABSTRACT

**Objectives:** Periostin is a matricellular protein, synthesized in the airway epithelium and induced by interleukin (IL)-4 and IL-13. The significance of periostin as a biomarker of T helper type 2 cell (Th2)-induced airway inflammation, and as a measure of the response to Th2-targeted therapy, has recently been highlighted. We explored the relationship between serum periostin and allergic rhinitis in Korean children.

**Methods:** Data for fifth and sixth grade children from six randomly selected elementary schools located in Jeju and Seogwipo City, Korea, were investigated. Serum periostin levels were determined by enzyme-linked immunosorbent assay. Sex, school grade, body mass index, and presence of allergic nasal symptoms were obtained via a self-reported survey and skin prick testing was performed.

**Results:** There were no significant differences between groups, when stratification was applied according to sex, grade, presence of atopy, and presence of allergic nasal symptoms. Sex and body mass index were significantly associated with serum periostin levels in multivariate linear regression analysis. However, allergic rhinitis was not associated with serum periostin levels.

**Conclusion:** Allergic rhinitis or allergic sensitization in Korean children did not influence serum periostin levels. Further studies are required to investigate the significance of serum periostin levels in pediatric allergic rhinitis.

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## 1. Introduction

Allergic rhinitis is a T helper type 2 cell (Th2)-mediated inflammatory disease characterized by mucosal eosinophilia, airway hyperresponsiveness, and mucus overproduction [1]. Symptoms of allergic rhinitis, such as watery rhinorrhea, sneezing, and nasal obstruction, impair quality of life and interfere with activities of daily living. With the progression of allergic rhinitis, the airways undergo structural and phenotypic changes, resulting in airway remodeling and include damage to epithelial cells, goblet cell metaplasia, subepithelial fibrosis, and smooth muscle hyperplasia and hypertrophy [2,3].

Periostin is an extracellular matrix protein originally isolated from an osteoblast cell line. Its production is induced by interleukin (IL)-4 and IL-13 in airway epithelial cells [4–7]. Periostin is also a regulator of fibrosis and collagen deposition. It has been recognized for its important role in myocardial repair and remodeling following myocardial infarction and periostin overproduction in the nasal mucosa has been reported to contribute to polyp formation [6,8].

Expression of periostin has been observed in bronchial epithelial tissue and periostin may play an important role in tissue remodeling in bronchial asthma [8]. Periostin may also be found in normal nasal tissues, however, it is expressed more strongly in the basement membranes of patients with allergic rhinitis than in that of control patients [9]. These findings support the concept that periostin is involved in Th2-driven inflammation and tissue remodeling in allergic rhinitis [9].

Therefore, it has been hypothesized that periostin may play a

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potential role in allergic disease, particularly in asthma. However, current evidence of the association between periostin and allergic rhinitis is scarce. This study examines the relationship between serum periostin and allergic rhinitis in Korean children.

## 2. Materials and methods

### 2.1. Study population

Six elementary schools located in Jeju and Seogwipo City, Jeju Island, were randomly selected and fifth and sixth grade children were identified. A study questionnaire was distributed and completed by students and parents. Skin prick tests (SPTs) and physical examination was performed by trained nurses in November 2014. Of a total of 691 children we excluded children who did not undergo the SPT or did not respond to the questionnaire. Children with a diagnosis of asthma or atopic dermatitis were also excluded. Furthermore, we examined the medication history of children over the 7 days preceding the SPT test and excluded children who were administered medicines, such as antihistamines or other drugs that could affect the result of the SPT. Finally, 140 children were excluded and 551 children were included in the analysis. The details of this study were explained to the students and parents, and written informed consents were obtained from legal guardians. This study was approved by the institutional review board of the Jeju National Hospital University, in accordance with the Declaration of Helsinki. Data collection was in accordance with the principle of respect for the confidentiality of patient records.

### 2.2. Assessment

Height and weight were measured by trained nurses. Body mass index (BMI) was calculated as weight (kg)/the square of height ( $m^2$ ). Sex, school grade, and presence of allergic nasal symptoms, were obtained from the self-reported questionnaire. The presence of allergic rhinitis symptoms was determined using the following question in the questionnaire: "Over the past 12 months, has your child ever had a problem with sneezing, or a runny, or a blocked nose when he/she did not have a cold or the flu?".

The history of asthma and atopic dermatitis was obtained using questionnaire: "Have you had a wheezing or whistling in the chest in the past 12 months?" and "Have you had an itching rash at any time in the past 12 months?", respectively.

For each subject, a 1.5 ml sample of blood was transferred to a cryotube for the serum periostin concentration measurement. Serum periostin was measured using enzyme-linked immunosorbent assay using human ELISA kit (AdipoGen, CA, USA) and Spectra MAX 190/USA (Molecular devices, CA, US) according to the manufacturer's instructions.

A total of 26 common aeroallergens were evaluated by SPT including: dermatophagoides pteronyssinus, dermatophagoides farinae, cat, citrus red mite, dog, cladosporium, alternaria, timothy grass, mugwort, barley, rapeseed, Japanese hop, Japanese cedar, rye grass, hen's egg (white), tuna, cow's milk, soya flour, mussel, yolk, shrimp, chicken meat, pork, peach, peanut, and wheat flour. All allergens, except citrus red mite and Japanese cedar, were purchased from Allergopharma (Reinbek, Germany). For Japanese cedar, the commercial allergen was purchased (Greer Laboratories Inc., Lenoir, NC, USA). Citrus red mite allergen was prepared as described in a previous study [10]. Histamine hydrochloride at a concentration of 1 mg/mL (Allergopharma, Reinbek, Germany) was used as the positive control, whereas a normal saline solution with 50% glycerin was used as the negative control. SPT was performed on the forearms by trained researchers using a 23-G lancet. Fifteen

minutes after SPT, the size of each wheal was calculated as the mean of (A) the longest diameter and (B) the diameter perpendicular to the first axis at the midpoint (i.e.,  $(A + B)/2$ ). The skin test was considered positive if an allergen elicited a wheal  $\geq 3$  mm. Allergic sensitization was established when the subject showed a positive skin test to one or more allergens.

### 2.3. Statistical analysis

Demographic data were presented as mean  $\pm$  standard error (SE). The differences in histamine wheal sizes were compared using the Student t-test and ANOVA test. The correlation between serum periostin level and BMI was analyzed by Spearman correlation test. Finally, linear regression analysis was used to show an independent effect after adjusting for confounding variables. SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses. A p-value  $< 0.05$  (two-tailed) was considered significant.

## 3. Results

Of 551 children included in the study, 267 were boys and 284 were girls. Demographic data of this study population are presented in Table 1. Among 276 children with allergic sensitization, 72 children showed sensitization to two or more allergens and 204 children showed sensitization to only one allergen. Dermatophagoides pteronyssinus (Dp) was a most common allergen which showed a positive skin test to 189 children. And, dermatophagoides farina (Df), Japanese cedar, and citrus red mite were followed (sensitization to 173, 73, and 58 children, respectively). 150 children showed sensitization to both of Dp and Df. 212 children among 276 sensitized children (76.8%) showed sensitization to Dp, Df or both. Mean serum periostin level in boys ( $51.9 \pm 13.0$  ng/ml) was significantly higher than in girls ( $47.5 \pm 13.3$  ng/ml). However, there were no significant differences between groups, when we stratified according to school grade, presence of atopy, and presence of allergic nasal symptoms (Table 1). When we analyzed the difference of mean serum periostin levels between groups divided by the number of sensitized allergens, there were also no significant differences of mean serum periostin levels between groups. (data not shown) Spearman's correlation test revealed a weak negative association between serum periostin levels and BMI ( $P < 0.001$ ,  $R = -0.182$ ) (Fig. 1).

We investigated the influence of allergic sensitization on serum periostin levels. According to the chi-square test, the rate of allergic sensitization was 56.9% (152/267) in boys and 43.7% (124/284) in girls. Rate of allergic sensitization was significantly higher in boys than in girls ( $p = 0.002$ ). Therefore, we stratified according to sex and then compared the mean serum periostin level between sensitized and non-sensitized children. There was no significant difference in serum periostin levels between the sensitized and non-sensitized children (boys or girls) (Fig. 2).

Subjects were divided into 4 groups, according to allergic sensitization and nasal symptoms (Fig. 3). The first group, with no allergic sensitization and no nasal symptoms, was defined as the control group. The second group, the non-allergic rhinitis group, included subjects with no allergic sensitization and with nasal symptoms. The third group, the subclinical allergy group, included subjects with allergic sensitization and no nasal symptoms. The fourth group, the allergic rhinitis group, included subjects with allergic sensitization and nasal symptoms. There were no significant differences in the mean serum periostin level among the 4 groups.

Multivariate linear regression analysis revealed that sex and body mass index were significantly associated with serum periostin levels. Conversely, allergic sensitization and/or allergic nasal

**Table 1**  
Demographic data.

| Variables               |       | N   | Serum periostin (ng/ml) | P-value* |
|-------------------------|-------|-----|-------------------------|----------|
| Sex                     | Boy   | 267 | 51.9 ± 13.0             | <0.001   |
|                         | Girl  | 284 | 47.5 ± 13.3             |          |
| Grade                   | Fifth | 277 | 49.8 ± 13.3             | 0.851    |
|                         | Sixth | 274 | 49.6 ± 13.4             |          |
| Allergic sensitization  | No    | 275 | 49.4 ± 13.6             | 0.697    |
|                         | Yes   | 276 | 49.9 ± 13.0             |          |
| Allergic nasal symptoms | No    | 334 | 50.0 ± 13.9             | 0.419    |
|                         | Yes   | 217 | 49.1 ± 12.3             |          |

\*p-value: calculated with t-test.

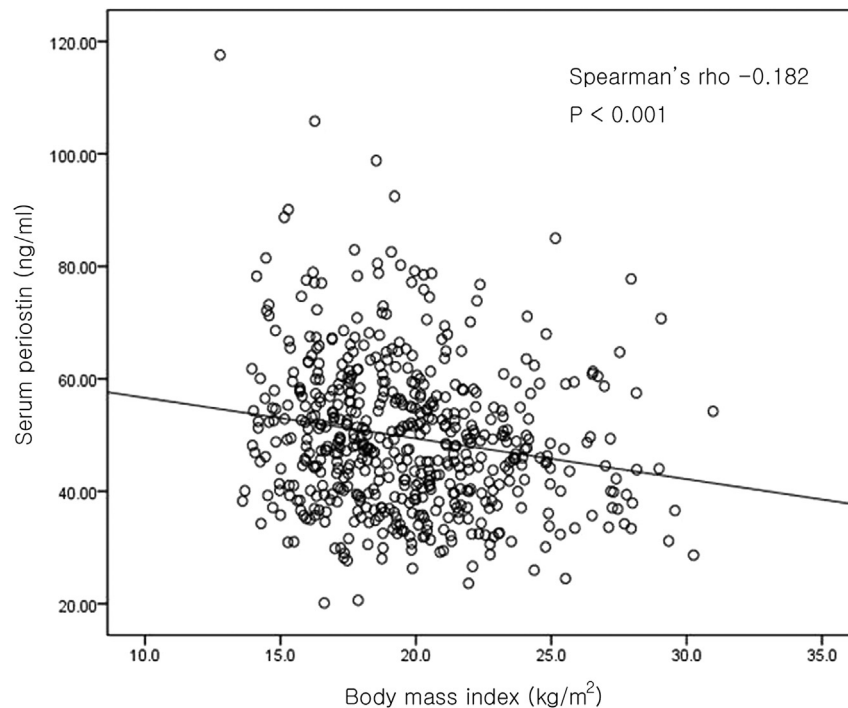


**Fig. 1.** Correlation between serum periostin and body mass index.

symptoms were not significantly associated with serum periostin levels (Table 2).

#### 4. Discussion

In recent decades, studies on periostin have been rapidly increasing. Periostin plays an important role in the development of bone, tooth, and heart valves, as well as in the healing process following myocardial infarction, and in the development of various tumors [11]. Increased periostin levels are found in conditions associated with increased cell division, cell turnover, cell invasion, and angiogenesis [12]. High levels of periostin are also associated with a range of inflammatory diseases. Periostin has been implicated in the physiopathology of multiple diseases, such as ankylosing spondylitis, idiopathic interstitial pneumonias, idiopathic pulmonary fibrosis, renal inflammation and fibrosis, and cancer [13–18]. Periostin has also been implicated in atopic conditions, such as dermatitis and rhinitis or rhinosinusitis [9,19]. Chronic rhinosinusitis is mediated by periostin and osteopontin, and these proteins induce a proliferative response within the extracellular matrix framework that leads to large scale remodeling of sinus histopathology [9].

Earlier reports showed that periostin is associated with the pathophysiology of asthma, through eosinophil recruitment, airway remodeling, and development of a Th2 phenotype [11]. Furthermore, there is evidence that it contributes to the increased expression of inflammatory mediators [20,21]. Periostin is also involved in the pathogenesis of bronchial asthma. Immunohistochemical analysis in asthma patients shows that periostin is deposited on thickened basement membrane, suggesting that it is a component of subepithelial fibrosis in bronchial asthma [22]. The role of periostin in allergic rhinitis is not fully understood. Ishida et al. observed periostin expression in the basement membrane, extracellular matrix, nasal polyp tissue, and infiltrating cells, by means of immunohistochemical staining [9]. Periostin levels were significantly higher in tissues derived from patients with allergic rhinitis, chronic rhinosinusitis with nasal polyps, or aspirin-induced asthma, than in control tissues [9].

Periostin could be a useful serum marker for a range of allergic diseases. Measurement of serum periostin levels, representing production of periostin in local inflammatory disease, may be a reasonable diagnostic approach for the following two reasons. First, periostin is likely to move easily from the affected lesions to blood vessels [22]. Second, basal serum levels of periostin are relatively

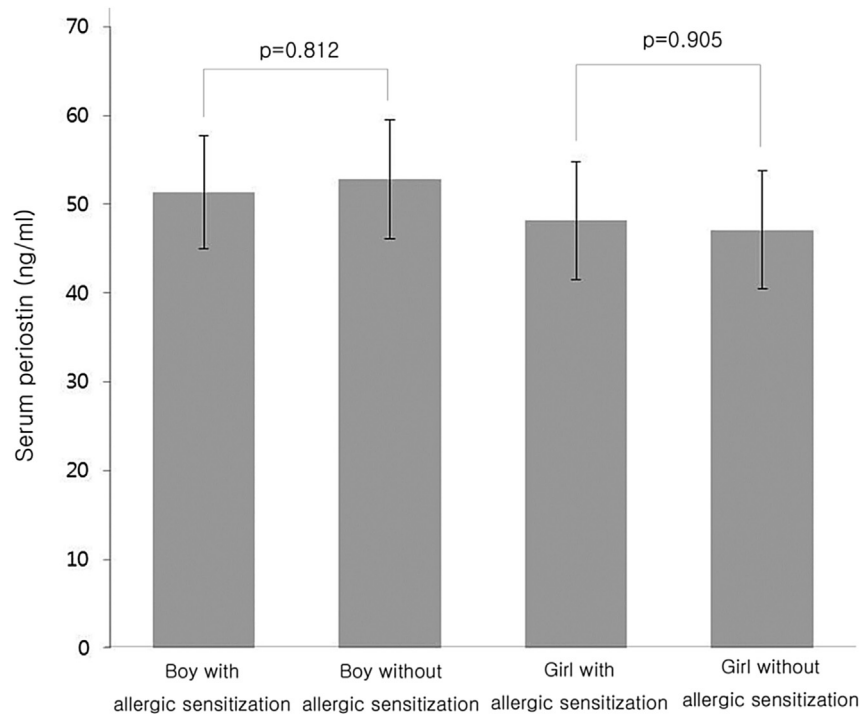


**Fig. 2.** Serum periostin level between groups with or without atopy in boys and girls. The error bar represents standard deviation.

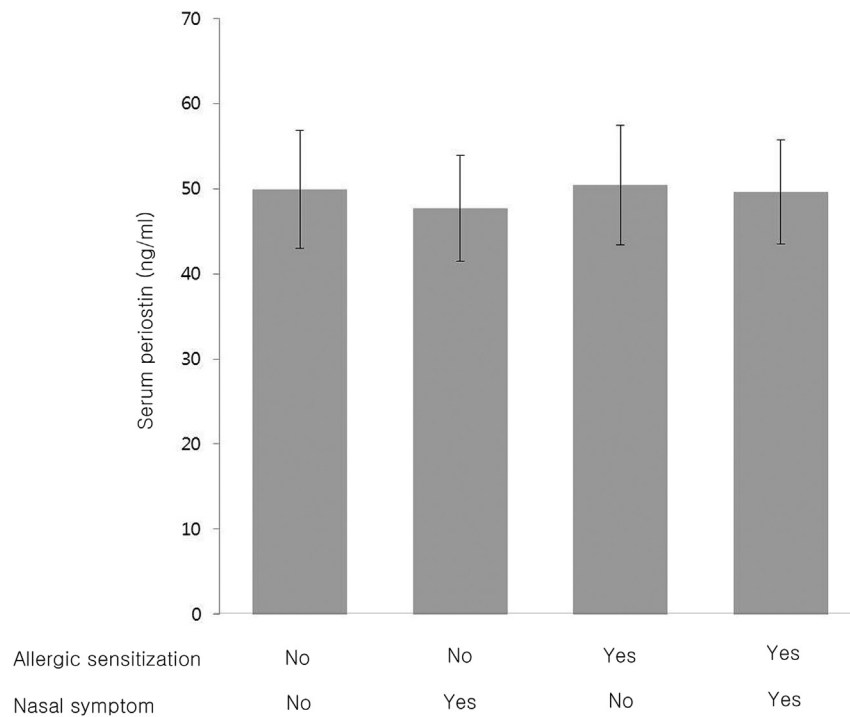


**Fig. 3.** Serum periostin level between groups with or without atopy and Allergic rhinitis symptoms. The error bar represents standard deviation.

low (~50 ng/ml) compared to other extracellular matrix proteins, such as fibronectin or vitronectin (200–300 µg/ml), and up-regulation of local production of periostin in affected lesions is clearly reflected in serum periostin levels [23]. Therefore, serum periostin is a biomarker of persistent airway eosinophilia, despite steroid treatment, in patients with severe asthma [24]. Also, previous research shows that periostin levels were significantly

elevated in atopic dermatitis patients [21].

However, little is known about the usefulness of serum periostin as a biomarker for allergic rhinitis, especially in childhood. To the best of our knowledge, there is only one published study on serum periostin and allergic rhinitis in children. Inoue et al. showed that serum periostin levels were not associated with various allergic diseases, including allergic rhinitis in children [25]. Our result

**Table 2**  
Multivariate linear regression analysis.

| Variables              |          |                   | Coefficient | 95% CI          |
|------------------------|----------|-------------------|-------------|-----------------|
| Sex                    | Boy      |                   | –           | –               |
|                        | Girl     |                   | –4.835      | –7.040 ~ –2.630 |
| Grade                  | Fifth    |                   | –           | –               |
|                        | Sixth    |                   | 0.738       | –1.482–2.958    |
| Allergic sensitization | Negative | Nasal Symptom (–) | –           | –               |
|                        | Negative | Nasal Symptom (+) | –1.358      | –5.219–2.503    |
|                        | Positive | Nasal Symptom (–) | –0.013      | –2.983–2.958    |
|                        | Positive | Nasal Symptom (+) | –0.372      | –3.037–2.294    |
| BMI                    |          |                   | –0.803      | –1.133 ~ –0.472 |

BMI: body mass index.

corroborate these findings. There was no difference in the mean serum periostin level between children with allergic rhinitis and those without allergic rhinitis. Moreover, allergic nasal symptoms and allergic sensitization did not affect serum periostin levels in Korean children. We suggest that there are several reasons why serum periostin was not elevated in children with allergic rhinitis. First, as observed by Inoue and co-workers, serum periostin levels in adults without allergic disease were significantly lower than in children without allergic disease [25]. Therefore, increased basal level of serum periostin may mask any increase in serum periostin associated with allergic disease [25]. Second, we propose that disease duration affects periostin levels and children may have had a shorter duration of disease compared to the adult population. Finally, the nasal cavity is a relatively smaller organ compared to the lung. Therefore, we suggest that the size of the affected organ could also be a potential determinant of serum periostin levels.

Currently the role of periostin in allergic inflammation is not fully understood nor is the association between periostin and allergic inflammation. Animal studies have demonstrated the protective role of periostin in allergic airway inflammation [26,27], whereas Blanchard et al. showed that periostin accelerates allergen-induced eosinophil recruitment in the lung and esophagus [4].

In our study, BMI was negatively associated with serum periostin levels in children. To date, there are no data on the association between serum periostin levels and BMI or obesity. However, Bolton et al. reported that the *periostin* gene was highly expressed in adipose tissue compared to other tissues [28]. This suggests that periostin may be involved in adipose tissue repair or that it is required for adipose tissue expansion, playing a role in extracellular matrix remodeling or adipocyte differentiation. However, our study found a negative correlation between serum periostin levels and BMI in Korean children. Further investigations are required to elucidate the association between obesity and serum periostin levels.

There are several limitations in our study. First, pediatric serum periostin may have been distorted by periostin secretion in growing bone tissue. Further studies are needed to clarify this issue. Second, we did not classify allergic rhinitis according to severity although disease severity could have affected serum periostin levels. Finally, we do not know with certainty how the increase in localized tissue periostin reflects serum periostin levels.

However, the strength of our study is the narrow population age range examined. Inoue and co-workers found that serum periostin levels increased with age [25]. Therefore, the narrow age range examined in our study potentially avoids the risk of a deviated result. Furthermore, we performed SPT, in addition to the questionnaire, to confirm a diagnosis of allergic rhinitis.

In conclusion, serum periostin was not associated with allergic rhinitis in Korean children. Further studies are required to confirm this finding conclusively.

## Author contributions

J.W.K. and J.H.K. designed the research; K.W.L., S.C.H., H.S.L., and J.H.K. analyzed the data; J.W.K. and D.Y.K. wrote the paper. J.W.K., J.H.K., and D.Y.K. revised the manuscript. J.W.K. had primary responsibility for final content. All authors read and approved the final manuscript.

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