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Original article

# Serum periostin is associated with body mass index and allergic rhinitis in healthy and asthmatic subjects

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*Abbreviations:*
ALT, alanine aminotransferase; AR, allergic rhinitis; AST, aspartate aminotransferase; BMI, Body mass index; BUN, blood urea nitrogen; Cre, creatinine; eGFR, estimate glomerular filtration rate; $FEV_1$, forced expiratory volume within 1 s; FPG, fasting plasma glucose; FVC, forced vital capacity; GGT, gamma-glutamyl transferase; HDL-C, high density lipoprotein cholesterol; IgE, immunoglobulin E; LDL-C, low density lipoprotein; NGSP, National Glycohemoglobin Standardization Program; TG, triglyceride; UA, uric acid

ABSTRACT

*Background:* Many studies have attempted to clarify the factors associated with serum periostin levels in asthmatic patients. However, these results were based on studies of subjects mainly characterized by high eosinophil counts, which may present as an obstacle for clarification in the identification of other factors associated with serum periostin levels. The aim of this study was to determine the factors associated with serum periostin levels in healthy subjects. We also assessed some factors in asthmatic subjects to confirm their extrapolation for management of asthma.
*Methods:* Serum periostin levels were measured in 230 healthy subjects. Clinical factors of interest included body mass index (BMI) and allergic rhinitis (AR). Additionally, we confirmed whether these factors were associated with serum periostin in 206 asthmatic subjects. We further evaluated several obesity-related parameters, such as abdominal fat distribution and adipocytokine levels.
*Results:* Smoking status, blood eosinophil count, total immunoglobulin E, and the presence of AR were associated with serum periostin in healthy subjects. There was a negative association between BMI and serum periostin in both healthy and asthmatic subjects, while there was a tendency of a positive association with AR in asthmatic subjects. There were no differential associations observed for subcutaneous and abdominal fat in relation to serum periostin in asthmatic subjects. Serum periostin was significantly associated with serum levels of adiponectin, but not with leptin.
*Conclusions:* Our results provided clarity as to the factors associated with serum periostin levels, which could be helpful in the interpretation of serum periostin levels in clinical practice.


## Introduction

Periostin is a secreted extracellular matrix protein that belongs to the fasciclin family. As a downstream molecule of interleukin (IL)-13, periostin has been proposed as a biomarker for the signature type-2 immune responses in asthmatic patients.[1–4] Functionally, periostin is a regulator of fibrosis and collagen

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deposition and has been recognized for its vital role in airway remodeling.[5] In this respect, high serum periostin levels have been associated with peripheral/airway eosinophilia, severe airflow limitation, and greater decline in forced expiratory volume (FEV) within 1 s ($FEV_1$) in asthmatic patients.[3,4,6,7] In addition, serum periostin levels are associated with a favorable response to asthma treatment including novel biologics such as anti-immunoglobulin E (IgE) and IL-13 monoclonal antibodies, suggesting that serum periostin could be used as a surrogate maker of successful asthma treatment.[8,9]

In addition to its role in asthma treatment, periostin has been found to be related to the physiopathology of numerous diseases, owing to its wide range of functions. For example, high levels of periostin expression have been detected in organs in certain diseases such as fatty liver disease, diabetes, and renal injuries.[10–12] Studies using mice deficient in periostin and its neutralizing antibody have suggested its role in the pathogenesis of the aforementioned diseases.[13,14] In addition, the local expression of periostin in the nasal mucosa of patients with allergic rhinitis (AR),[15] which occurs in approximately 30% of Japanese adults, has been reported.[16,17] These studies suggest that serum periostin levels are influenced by several factors related to common diseases such as metabolic disease, liver and renal impairment, and AR.

To date, numerous studies have attempted to clarify the clinical characteristics and phenotypes associated with elevated serum periostin levels in asthmatic patients.[2–4,6] However, these studies were conducted in patients with asthma, which may confound one's ability to determine other factors associated with serum periostin levels. Considering the vast heterogeneity of eosinophilic inflammation in patients with asthma and the strong association between asthma and serum periostin levels, other factors that impact serum periostin levels among patients with asthma may have been masked in these studies. Therefore, it is necessary to investigate the factors associated with serum periostin in non-asthmatic subjects. Based on this concept, Caswell-Smith *et al.* have reported several factors associated with serum periostin levels in subjects without asthma or chronic obstructive pulmonary disease (COPD).[18]

We have conducted case–control studies to identify novel genetic factors and biomarkers of asthma have recruited subjects without pulmonary diseases or malignant diseases as controls for patients with asthma.[19–21] In the present study, using these subjects, we first attempted to identify factors associated with serum periostin levels. We were particularly interested in the association between serum periostin levels and body mass index (BMI), and AR, both of which are significant comorbidities associated with asthma. Therefore, we also confirmed whether similar associations were found in asthmatic subjects to determine their clinical utility in the management of asthmatic subjects. In addition, in order to further clarify the relationship between obesity and periostin levels, we evaluated several obesity-related indices such as subcutaneous/abdominal fat density, as assessed by computed tomography (CT), and blood adipocytokine levels.

## Methods

This study was approved by the Ethical Review Boards of Hokkaido University (14-057), Hokkaido University Hospital (009-0205), and JR Sapporo Hospital (2012-5). Written informed consent was directly obtained from study subjects by doctors.

### *Non-asthmatic subjects*

Healthy Japanese subjects who underwent their annual health check at the JR Sapporo Hospital (Sapporo, Japan) were recruited for enrollment into this study. Subjects were asked to answer the Japanese edition of the European Community Respiratory Health Survey (ECRHS) questionnaire,[16,22,23] as summarized in the online supplement. Subjects who had any of the following conditions were excluded from the study: history of any pulmonary diseases or respiratory symptoms (Questions 1–6,8,10,11, part of 15 and 16); abnormal chest X-ray shadow, evaluated by respiratory physicians; percentage of predicted vital capacity (VC) < 80%; ratio of $FEV_1$ to forced vital capacity ($FEV_1$/FVC) < 70%; presence or past history of malignant diseases. The remaining subjects were enrolled in the study and classified as “non-asthmatic subjects”.

### *Asthmatic subjects*

Recruitment of asthmatic subjects has been previously described.[4,24] This population consisted of Japanese patients with asthma who had been enrolled in the Hokkaido-based Investigative Cohort Analysis for Refractory Asthma (Hi-CARAT). This study was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry system (UMIN ID 000003254) (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000003917). Diagnosis of severe asthma was based on the American Thoracic Society criteria for refractory asthma published in 2000[25], with slight modifications.[4,24]

### *Smoking status*

Patients were categorized into three groups: current continuous smokers (Current; Affirmative question, Do you now smoke, as of 1 month ago?), former smokers who had stopped smoking for a minimum of 1 month before the initial visit (Ex; Affirmative question of Have you ever smoked for as long as a year?), and lifetime non-smokers (Never) (Supplementary Methods). In addition, we evaluated cumulative smoking exposure by calculating pack-year (PY) by questions “How many cigarettes to you smoke every day?” “How many cigarettes had you being smoking?” (From years old to years old per day)” (Supplementary Methods).

### *Anthropometric measurements*

Subjects were weighed wearing minimal clothes and without shoes; weight was rounded to the nearest 0.1 kg. Additionally, height was measured to the nearest 0.1 cm. BMI was calculated as weight (kg) divided by the squared height (m). A clinical research coordinator (CRC) or nurse measured the waist circumference (WC) at the navel of each subject in a standing position, rounding to the nearest 0.1 cm, using the methods proposed by the Japan Society for the Study of Obesity.[26]

### *Definition of allergic rhinitis*

Presence of rhinitis symptoms was assessed using questionnaires, according to the Practical Guideline for the Management of Allergic Rhinitis in Japan 2009.[27] Subjects were asked, “Do you have any nasal allergies including hay fever?” (Supplementary Methods).

### *Analysis of blood samples*

Blood samples were collected for testing after fasting for at least 12 h. Peripheral blood eosinophil counts were obtained from standard complete blood counts, which were performed at the laboratory division of Hokkaido University Hospital. Total serum IgE levels (IU/mL) and IgE responses to commonly inhaled allergens, including *Dermatophagoides farinae*, grass pollens, animal dander, and molds, were determined. Atopy was defined on the

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