Letter to the Editor

Clinical implication of the serum periostin level for differentiating phenotypes of NSAID hypersensitivity

Dear Editor,

Nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity is a common drug allergy, in which 2 major phenotypes, respiratory (aspirin-exacerbated respiratory disease [AERD]) and cutaneous (aspirin-exacerbated cutaneous disease [AECD]) or aspirin-intolerant acute urticaria (AIAU) types, are noted.1 Typical symptoms of the respiratory type of NSAID hypersensitivity are dyspnea, cough, and rhinorrhea, while those of the cutaneous type are urticaria and angioedema. However, it is sometimes confused to establish in patients with chest tightness or dyspnea after ingestion of NSAIDs because the symptoms may originated from bronchoconstriction of AERD or from angioedema of AIAU.2 Periostin is an extracellular matrix protein and structurally homologous with fasciclin I, an insect adhesion molecule. The serum periostin level correlates well with eosinophilic airway inflammation and considered a prognostic factor for the treatment of lebrikizumab (a monoclonal antibody to IL-13).3 Recent studies have shown that periostin contributes to tissue remodeling and is increased in the serum or the lesional tissue of allergic rhinitis/chronic rhinosinusitis, atopic dermatitis, and asthma.4-7 In addition, the serum periostin level is significantly higher in AERD patients than in aspirin-tolerant asthmatic patients because AERD shares Th2-mediated pathogenesis with eosinophilic asthma.8

We hypothesized that the serum periostin level would differ between respiratory and cutaneous types of NSAID hypersensitivity because remodeling occurs in the respiratory type of hypersensitivity, but not in the cutaneous type. In the present study, we compared serum periostin levels between respiratory and cutaneous types of NSAID hypersensitivity to evaluate the serum periostin level as a biomarker for differentiating between phenotypes of NSAID hypersensitivity.

A total of 326 adult patients with NSAID hypersensitivity and 87 healthy normal control (NC) subjects were included in the study. Serum samples were obtained with written informed consent. The samples were frozen at −70 °C after collection and thawed immediately before use. Clinical data were obtained from the registry database and electronic medical records reviewed by the allergy specialists. The protocols used in this study were approved by the Institute Review Board of Ajou University Hospital. According to clinical data, NSAID hypersensitivity was classified into AERD, AECD, and AIAU by the clinicians at the Department of Allergy and Clinical Immunology. AERD was defined by the presence of recurrent typical clinical history (development of respiratory symptoms after ingestion of aspirin or other NSAIDs) and/or positive results to the lysine-aspirin bronchoprovocation test. AECD referred to a chronic urticaria exacerbated after aspirin/NSAID exposure, while acute urticaria was provoked only after ingestion of the drug in AIAU.9 Serum periostin levels were measured by using a proprietary sandwich ELISA (Shino-Test, Kanagawa, Japan) on duplicated samples as previously described (see Measurement of serum periostin).10 Periostin levels were compared among individual groups using Student’s t-test and analysis of variance (ANOVA). Receiver operating characteristic (ROC) curve analysis was performed to determine a discrimination threshold between respiratory and cutaneous types of NSAID hypersensitivity with area under the curve (AUC).

Among 326 NSAID hypersensitivity patients, 45.7% (n = 149) were of the respiratory type and 54.3% (n = 177) were of the cutaneous type, which included AEC (n = 111) and AIAU (n = 66). The mean ages were 45.5 ± 13.3, 43.3 ± 11.7, and 44.0 ± 13.0 years in AERD, AECD, and AIAU, respectively, and the proportions of male patients were 33.6%, 39.6%, and 41.5%, respectively. In NC, the mean age was 27.3 ± 6.3 years, and 56.3% of the subjects were male. The mean serum periostin levels were 82.6 ± 38.8, 40.4 ± 32.5, 38.6 ± 28.9, and 46.2 ± 29.0 ng/mL in AERD, AECD, AIAU, and NC, respectively. The serum periostin levels were significantly higher in AERD than in AECD (P < 0.001), in AIAU (P < 0.001), and in NC (P < 0.001). However, there were no significant differences in serum periostin levels between AECD and AIAU (P = 0.708), between AEC and NC (P = 0.195), and between AIAU and NC (P = 0.110) (Fig. 1). ROC curve analysis showed that the serum periostin level could differentiate between respiratory and cutaneous types of NSAID hypersensitivity (AUC = 0.826, P < 0.001) because the serum periostin levels were significantly higher in the respiratory type (82.6 ± 38.8 ng/mL) than in the cutaneous type (39.7 ± 31.1 ng/mL) (P < 0.001). The cut-off level was 42.5 ng/mL, with a sensitivity of 93.3% and a specificity of 61.0% (Fig. 2).

In the present study, we found that the serum periostin levels were significantly higher in the respiratory type of NSAID hypersensitivity than in the cutaneous type and could discriminate between these 2 phenotypes. This result has 3 clinical implications. First, serum periostin may be used to discriminate between types of NSAID hypersensitivity in patients who present with chest tightness or dyspnea with unknown underlying disease such as asthma and the symptoms are vague to distinguish the exacerbation of AERD or angioedema. Second, asthma patients with high serum periostin levels would not use NSAID because of adverse drug reactions, but this is not applied in chronic urticaria. Third, a higher
inflammation with tissue remodeling. Some investigations have demonstrated that subepithelial fibrosis, the most significant finding of airway remodeling, might be caused by periostin. IL-4 and IL-13 stimulate secretion of periostin from lung fibroblasts, and the periostin binds to extracellular matrix proteins. Thereafter eosinophils stimulated by IL-5 migrate to areas of high periostin density in an asthmatic airway through adhesion of eosinophil’s αMβ2, subsequently resulting in tissue damage and fibrosis. In conclusion, the serum periostin level can be a useful biomarker for predicting the phenotype of AERD among NSAID hypersensitivity patients. It may help clinicians determine types of NSAID hypersensitivity and predict prognosis. In addition, asthma patients with high serum periostin levels would not use NSAID, unlike AECD.

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Conflict of interest
JO is an employee of Shino-Test Corporation. KI received research funding from Shino-Test Corporation, Chugai Pharmaceutical, and consultant fee from Chugai Pharmaceutical, Aqua Therapeutics. The rest of the authors have no conflict of interest.

Mi-Ae Kim a, Moon Kyung Yoon b, Young-Soo Lee b, Kenji Izuhar a, Shoichi Ohta d, Junya Ono e, Ji-Hye Kim b, Ga Young Ban b, Young-Min Ye b, Hae-Sim Park h, i

a Department of Pulmonology, Allergy and Critical Care Medicine, CHA Bundang Medical Center, CHA University, Seongnam, South Korea 

b Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, South Korea 

c Department of Laboratory Medicine, Saga Medical School, Saga, Japan 

d Department of Pulmonology, Allergy and Critical Care Medicine, CHA Bundang Medical Center, CHA University, Seongnam, South Korea 

e Division of Medical Biochemistry, Department of Biomolecular Sciences, Saga Medical School, Saga, Japan 

f Department of Laboratory Medicine, Saga Medical School, Saga, Japan 

g Shino-Test Corporation, Kanagawa, Japan 

h Department of Biomedical Science, Ajou University Graduate School, Suwon, South Korea 

i Corresponding author. Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Wonchondong San 5, Youngtongku, Suwon 443-721, South Korea. 

E-mail address: hspark@ajou.ac.kr (H.-S. Park).

References

