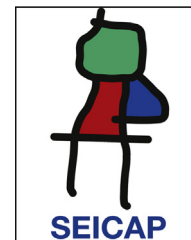




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## ORIGINAL ARTICLE

# Level of serum neutrophil gelatinase-associated lipocalin in childhood asthma



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### KEYWORDS

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### Abstract

**Background:** The role of neutrophil gelatinase-associated lipocalin (NGAL) in childhood asthma remains unknown. This study aimed to measure the serum levels of NGAL in children with asthma and to investigate the correlation between NGAL and transforming growth factor beta 1 (TGF- $\beta$ 1), a good indicator of airway remodeling in children with asthma.

**Methods:** This prospective, cross-sectional study was conducted on 75 children. Serum NGAL and TGF- $\beta$ 1 concentrations were measured by the ELISA method. Complete blood count, high sensitive C reactive protein (hsCRP), eosinophil cationic protein (ECP), and total serum IgE were investigated in the study population. Atopy in the asthma group was investigated using a skin prick test and specific IgE measurements.

**Results:** Forty-three asthmatic children and 32 healthy children were enrolled in the study. Total eosinophil numbers, white blood cell count, total serum IgE levels and ECP levels were significantly higher in the asthma group than in the control group ( $p < 0.05$ ). Similarly, serum TGF- $\beta$ 1 levels were significantly higher in children with asthma ( $p = 0.012$ ). The difference in NGAL levels between the groups was insignificant ( $p = 0.268$ ). NGAL levels did not show a significant correlation with total IgE, ECP, eosinophil numbers and TGF- $\beta$ 1 levels ( $p > 0.05$ ).

**Conclusion:** As a conclusion, while elevated TGF- $\beta$ 1 levels in children with asthma might be regarded as an indicator of airway remodeling, we did not find a similar prediction strength for NGAL. Further studies are required to better identify the role of NGAL in childhood asthma and to determine its potential use as a clinical marker.

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## Introduction

Asthma is one of the most common chronic diseases, estimated to be affecting 300 million people worldwide, with an increasing prevalence especially among children. Asthma is a clinical diagnosis based on episodic symptoms and variable airways obstruction. It is also characterized by variable degrees of chronic inflammation and structural alterations in the airways. These structural alterations, generally called airway remodeling, encompass complex changes in composition, content, and organization of the various cellular and molecular constituents of the airway wall. The most important abnormalities are epithelial detachment, goblet cell hyperplasia, subepithelial thickening, hyperplasia and hypertrophy of airway smooth muscle, bronchial gland enlargement, angiogenesis, and alterations in the extracellular matrix component.<sup>1-3</sup>

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa glycoprotein first identified as a matrix protein of specific granules of human neutrophils.<sup>4</sup> NGAL is secreted by neutrophils<sup>4</sup> and other cells such as respiratory<sup>5</sup> and intestinal<sup>6</sup> epithelial cells, vascular endothelial cells,<sup>7</sup> adipose tissue,<sup>8</sup> macrophages<sup>9</sup> and tubuli cells in the kidneys.<sup>10</sup> The role of extracellular matrix proteins in the process of airway remodeling is well known. Matrix metalloproteinase-9 (MMP-9) and NGAL have been shown to be particularly associated with lung capacity and clinical severity. Several studies performed on patients with asthma, pulmonary emphysema, chronic obstructive pulmonary disease (COPD) revealed increased MMP-9 and NGAL levels in bronchoalveolar lavage (BAL) fluid samples, probably as a result of structural alterations in the airways.<sup>11-15</sup> Additionally, a recent study reported significantly higher plasma NGAL levels in COPD patients than in control patients.<sup>16</sup>

The role of NGAL as a potential marker of disease severity in childhood asthma remains unknown. Research involving invasive bronchoscopy techniques in young children is limited; hence studies have focused on systemic markers indicating the possible structural alterations in the airways. In the present study we investigated the association between serum NGAL levels and clinical and laboratory parameters in children presenting with asthma. Additionally, we investigated the correlation between NGAL and transforming growth factor beta 1 (TGF- $\beta$ 1), a good indicator of airway remodeling in children with asthma.<sup>17,18</sup>

## Materials and methods

### Study subjects

This prospective, cross-sectional study was conducted on 75 children, 43 of whom suffered from asthma presenting with wheezing to the Fatih University pediatric allergy outpatient clinic and 32 of whom were healthy controls. The asthma group included children of ages  $\leq 6$  years, with at least four wheezing attacks during the previous year, and ages  $> 6$  years who were diagnosed clinically and functionally according to GINA criteria.<sup>2</sup> Children of similar age and gender with no history of allergic disease or wheezing were selected as the control group. Healthy children were chosen among those being brought for routine controls. Those with

chronic diseases (e.g. malnutrition, anatomic malformation of the respiratory system, chronic lung disease, heart disease, gastro-esophageal reflux disease, cystic fibrosis) were excluded from the study.

Venous fasting blood samples were collected into Vacuette tubes (Greiner Bio-One, Monroe, NC) and centrifuged at  $3000 \times g$  for 15 min at  $4^\circ\text{C}$ . Serum samples were stored at  $-80^\circ\text{C}$  for not more than 6 months. Levels serum of TGF- $\beta$ 1 was measured by the ELISA (enzyme linked immunosorbent assay) method using a ELX-800 system (RayBiotech, Norcross, GA, US). Serum NGAL concentrations were determined with BioVendor Human Lipocalin-2/NGAL ELISA kit (BioVendor GmbH, Heidelberg, Germany). The limit of detection for this assay was 0.02 ng/mL with total imprecision (as CV)  $< 8\%$  at concentrations of 23.63–68.19 ng/mL. The antibodies used in this ELISA are specific for human lipocalin-2. Complete blood count was investigated with the LH-780 system (Beckman Coulter Diagnostics, Image 8000, Brea, CA, USA). Levels of high sensitive C reactive protein (hsCRP) were measured by turbidimetric assay method using a Roche P 800 modular system (Hitachi, Tokyo, Japan). Levels of eosinophil cationic protein (ECP) were measured by the chemiluminescent assay method using an Immulite 2000 systems (Siemens, Llanberis, Gwynedd, UK). The eosinophil counts were measured by LH-780 system (Beckman Coulter, Mervue, Galway, Ireland). Levels of total serum IgE were measured by the ECLIA (electrochemiluminescence) method using a ELX-800 system (DIAsource, Nivelles, Belgium).

Atopy in the asthma group was investigated using a skin prick test (SPT) and specific IgE (sIgE) measurements. A test was considered positive if the SPT results demonstrated a wheal with a mean diameter of at least 3 mm greater than that of a saline control. Each child was tested with a core battery of allergens (e.g. dust mite, cockroach, cat, dog, mold, grass, tree, weed, milk, egg, peanut) and a clinic-specific battery of locally relevant allergens (ALK Abelló, Hørsholm, Denmark). Spirometry (Vmax encore; VIASYS Healthcare Inc., Conshohocken, PA) and bronchodilator reversibility were defined as greater than a 12% or 200 ml change from baseline FEV<sub>1</sub>. These parameters were measured according to the GINA criteria.<sup>2</sup>

### Statistical analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows, version 16.0 (SPSS Inc., Chicago, IL, United States). All the continuous values were presented as mean  $\pm$  standard deviation (SD). The categorical values were presented as  $n$  (%). The homogeneous distribution of the data was evaluated using the Kolmogorov–Smirnov test. Homogeneity of variance was evaluated by the Levene test. In the comparisons of the groups, Student  $t$ -test was used. The chi-square test was used for categorical variables. Correlation between the independent parameters was investigated by bivariate (Pearson) correlation analysis. A  $p$ -value of less than 0.05 was considered as statistically significant.

The study was initiated upon approval by the Local Ethics Committee of Fatih University in accordance with the Helsinki Declaration. The written informed consent of the parent(s) of each subject was also obtained before the study.

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