Research Square

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Serum NGAL is elevated in patients with asthma and persistent airflow obstruction

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Research article

Keywords: Asthma, airflow obstruction, NGAL, airway remodeling

Posted Date: April 13th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-22279/v1

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Abstract

Background: Neutrophilic airway inflammation is one of the features of severe asthma. Neutrophil gelatinase-associated lipocalin (NGAL), or lipocalin-2, is a glycoprotein associated with neutrophilic inflammation and can be detected in blood. Recently, blood NGAL levels have been reported to be elevated in chronic obstructive pulmonary disease. However, the clinical significance of serum NGAL levels in patients with asthma has not been elucidated. The aim of this study was to explore the association between serum NGAL level and clinical parameters in patients with asthma.

Methods: Sixty-one non-smoking people with stable asthma were enrolled in this study. All patients underwent blood collection and pulmonary function tests. The associations between serum NGAL levels and clinical parameters were analyzed retrospectively.

Results: Serum NGAL levels in patients with asthma and obstructive ventilatory disorder were higher than those in patients with asthma without obstructive ventilatory disorder (76.4 ± 51.4 ng/mL vs 39.3 ± 27.4 ng/mL, p=0.0019). Serum NGAL levels were correlated with forced expired flow at 50% of vital capacity %predicted and forced expired flow at 25% of vital capacity %predicted (r=-0.3373, p=0.0089 and r=-0.2900, p=0.0234, respectively). Results of a multiple regression analysis demonstrated that serum NGAL level was independently associated with obstructive ventilatory disorder.

Conclusion: Serum NGAL levels were elevated in patients with asthma and obstructive ventilatory disorder. NGAL may be involved in airway remodeling possibly mediated by neutrophilic inflammation in asthma.

Background

Asthma is defined as a disease characterized by chronic airway inflammation, which is considered to be a response to various allergens, such as fungi, house dust, and insects [1]. Although asthma is mainly caused by Th2 cells and eosinophilic inflammation [2], several phenotypes of asthma have been recognized and are based on clinical, pathophysiological, and demographic characteristics [3]. According to an analysis of airway inflammation using sputum, asthma is classified into four subtypes by the proportion of eosinophils and neutrophils in the sputum: eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic [4].

A recent study showed that the number of neutrophils in bronchoalveolar lavage (BAL) fluid of patients with severe asthma was higher than that in patients with non-severe asthma [5]. Moreover, patients with asthma and neutrophilic airway inflammation are known to be resistant to treatment with steroids and have greater airflow obstruction [6-8]. There have also been reports demonstrating that the degree of neutrophilic airway inflammation correlates with that of airflow obstruction [9]. Thus, airway neutrophilic inflammation is thought to be one of the clinical features of severe asthma [10].

Neutrophil gelatinase-associated lipocalin (NGAL), or lipocalin-2, is a member of the lipocalin family [11]. It is a major constituent of neutrophil secondary granules and is secreted mainly by activated neutrophils. The role of NGAL has been well explored in the field of innate immunity. NGAL was reported to exert an antimicrobial effect by sequestrating iron-loaded bacterial siderophores [12] and to take part in neutrophilic function. Interestingly, NGAL can be detected in blood. Thus, the clinical significance of blood NGAL level has been evaluated as a biomarker of neutrophilic inflammation in several diseases [13-15].

NGAL has recently attracted attention as an indicator of neutrophilic inflammation in chronic obstructive pulmonary disease (COPD), which is a chronic inflammatory airway disease characterized by neutrophilic inflammation and poorly reversible airway obstruction [13]. In fact, plasma NGAL levels have been reported to be elevated in COPD and associated with frequent exacerbations and hypoxia [16]. However, in asthma, the clinical significance of blood NGAL level has not been elucidated. Given that neutrophilic airway inflammation is one of the features of severe asthma, blood NGAL level may have an impact on the understanding of the mechanisms and management of asthma. Given what is known about NGAL, we hypothesized that blood NGAL level was associated with asthma severity. We therefore measured serum NGAL levels and explored the association between serum NGAL levels and clinical parameters in patients with asthma.

Methods

Study design and patients

This study included 61 outpatients with asthma aged 20 years or older and treated at Tokyo Medical University Hospital from January 2011 to December 2017. The diagnosis of asthma was made using the criteria from the Global Initiative for Asthma (GINA) guideline [17]. None of the patients had any respiratory diseases other than asthma. Patients who had experienced an asthma attack within 1 year before blood collection and patients who had a history of smoking were excluded. We retrospectively analyzed the relationship between serum NGAL levels and clinical parameters. This study was approved by the ethics committee of Tokyo Medical University and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from each patient.

Laboratory and clinical measurements

Serum samples were collected from all patients and were stored frozen at -80°C until they were analyzed for NGAL level. Serum NGAL and periostin levels were measured using an ELISA kit (R&D Systems Inc., McKinley, NE) according to the manufacturer's instructions. Peripheral blood eosinophil counts and serum IgE levels were evaluated at the time of blood collection. Pulmonary function tests were performed with the following spirometers: CHESTAC-7800 and CHESTAC-8800 (CHEST, Tokyo, Japan), in accordance with GINA recommendations [17]. Obstructive ventilatory disorder was defined as forced expiratory volume in 1 second (FEV_1) / forced vital capacity (FVC) of less than 70%.

Statistical analysis

A p-value of less than 0.05 was considered to be statistically significant. All values were expressed as the mean ± standard deviation (SD). Categorical variables were compared by Fisher's exact test. The Mann-Whitney U-test was performed to analyze differences between groups. Correlations were analyzed using Spearman's correlation test. A multiple regression analysis was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). Serum NGAL level was used as a dependent variable, whereas age, sex, duration of asthma and obstructive ventilatory disorder were used as independent variables. All other statistical analyses were performed using the GraphPad Prism software program (GraphPad, San Diego, CA).

Results

Patient characteristics

Sixty-one non-smoking patients with stable asthma were enrolled in this study. The mean age was 57.4 years, with a range between 24 and 83 years. The patients included 20 men (33%) and 41 women (67%). Seven patients (8%) had childhood-onset asthma. Regarding the GINA treatment step, 33 patients were treated with step 2, 26 patients were treated with step 3, and two patients were treated with step 4. The mean duration of asthma was 13.4 ± 7.0 years, with a range between 5 and 35 years.

The mean peripheral blood eosinophil count was 3.9 ± 3.4 %. The mean levels of IgE and serum periostin were 576.8 ± 1009.3 IU/mL and 79.3 ± 41.6 pg/mL, respectively. The mean FVC was 3.2 ± 1.0 L, and the mean FEV_1 was 2.3 ± 0.8 L. The mean FEV_1/FVC was 71.3 ± 10.0 %. The mean FVC %predicted and FEV_1 %predicted were 110.3 ± 19.3 % and 98.9 ± 19.5 %, respectively. The characteristics of the enrolled patients are shown in Table 1.

Relationship between serum NGAL level and clinical parameters

Serum NGAL levels were positively correlated with age and duration of asthma (r=0.2706, p=0.0349 and r=0.2673, p=0.0373, respectively), whereas serum NGAL levels were not correlated with peripheral blood eosinophil counts, IgE level, or serum periostin level, which are biomarkers of Th2 inflammation (Table 2). There were no significant differences between men and women with respect to serum NGAL levels. There were also no significant differences in serum NGAL levels between patients treated with GINA step 2 and patients treated with GINA step 3 or 4.

Serum NGAL levels of patients with obstructive ventilatory disorder were significantly higher than those of patients without obstructive ventilatory disorder (76.4 ± 51.4 ng/mL vs 39.3 ± 27.4 ng/mL, p=0.0019) (Figure 1). Serum NGAL levels were negatively correlated with forced expired flow at 50% of vital capacity (FEF_{50}) %predicted and forced expired flow at 25% of vital capacity (FEF_{25}) %predicted (r=-0.3373, p=0.0089 and r=-0.2900, p=0.0234, respectively), whereas serum NGAL levels did not correlate with FEV_1

%predicted, suggesting that serum NGAL level reflects impairment of the distal airway rather than of the proximal airway (Figure 2).

Multiple regression analysis of serum NGAL level

We performed a multiple regression analysis to assess the confounder effects of age and duration of asthma on the relationship between serum NGAL level and obstructive ventilatory disorder. After adjustment for these variables, we found that serum NGAL level was independently associated with obstructive ventilatory disorder (Table 3).

Discussion

We demonstrated in this study that serum NGAL levels of non-smoking people with stable asthma and obstructive ventilatory disorder were higher than those of people with asthma without obstructive ventilatory disorder. There were negative correlations between serum NGAL level and spirometric variables related to the distal airway. Although serum NGAL levels were also correlated with age and duration of asthma, we confirmed that serum NGAL level was independently associated with obstructive ventilatory disorder by performing a multiple regression analysis.

The role of NGAL has been investigated with respect to neutrophilic inflammation associated with smoking in the field of respiratory medicine. Blood NGAL level has been explored in COPD, which is mainly caused by smoking and characterized by neutrophilic airway inflammation. Plasma NGAL levels in patients with COPD were reported to be higher than those in healthy subjects [16]. Among people with COPD who smoke, serum NGAL levels were correlated with serum levels of neutrophil elastase [18]. Moreover, a previous study showed a tendency for plasma NGAL levels to be higher in patients with asthma-COPD overlap (ACO) than in people with only asthma [19]. People with asthma who have a long smoking history may develop ACO [20,21]. In such cases, plasma NGAL levels have been suggested to be useful for identifying patients in whom a change was observed from asthma alone to ACO [22-24].

Regarding the relationship between airflow obstruction and serum NGAL level, serum NGAL levels in patients with severe/very severe COPD (GOLD 3/4) were reported to be higher than those in patients with mild/moderate COPD (GOLD 1/2), indicating that serum NGAL level may have some associations with airflow obstruction [13]. In the present study, we found that serum NGAL levels were associated with airway obstruction, especially of the distal airway, even in non-smoking patients with stable asthma. The mechanism for explaining how serum NGAL level is affected by airflow obstruction is unknown. However, neutrophilic airway inflammation is thought to be involved in airflow remodeling, which is a cause of persistent airflow obstruction in asthma. Thus, we speculate that NGAL is involved in airway obstruction via airway remodeling caused by neutrophilic inflammation.

Airway remodeling is generally a result of chronic airway inflammation in people with asthma. Mucosal gland hyperplasia, airway smooth muscle hypertrophy, and reticular basement membrane thickening are typical features of airway remodeling in asthma. These pathological changes cause progressive and

irreversible decline in lung function [25]. Although neutrophils play an important role in pathogen clearance, persistent airway neutrophilia and the consequent increase in protease secretion cause airway remodeling [26].

NGAL has been reported to potentially promote airway remodeling through epithelial-mesenchymal transition (EMT). According to an in vitro study, NGAL down-regulates E-cadherin expression and up-regulates α-SMA expression in 16HBE cells via the WNT/glycogensynthase-3β (GSK-3β) pathway. NGAL has also been reported to promote the proliferation and migration of human bronchial smooth muscle cells (HASMC) [27].

There are several limitations of this study. First, this was a retrospective, single-center study with a small number of patients. Second, we did not evaluate the potential effect of second-hand smoke exposure. There is a possibility that our results were affected by second-hand smoke exposure. Third, we did not evaluate the number of neutrophils in the sputum or BAL fluid. Thus, the association between serum NGAL level and neutrophilic airway inflammation was not evaluated in this study.

This is the first report to evaluate the relationship between serum NGAL levels and clinical parameters in patients with asthma. We found that serum NGAL levels were elevated in non-smoking patients with stable asthma and obstructive ventilatory disorder and were correlated with variables related to the distal airway. Our findings suggest that NGAL is involved in airway remodeling of the distal airway and possibly mediated by neutrophilic inflammation. Clinically, serum NGAL level is a proposed candidate biomarker of persistent airway obstruction in asthma. Additional studies are required to further analyze the association between serum NGAL level and neutrophilic airway inflammation and remodeling in asthma.

Declarations

Funding: None

Competing Interest: The authors declare that they have no conflict of interest.

Ethics approval and consent to participate: Written informed consent was obtained from each patient. Approval was obtained from the ethics committee of Tokyo Medical University (No. T2019-0108). The procedures used in this study adhere to the tenets of the Declaration of Helsinki

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: Not applicable

Availability of data and materials: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability: Not applicable

Authors' contributions: All authors contributed to the study conception and design. Sample collection, data collection and analysis were performed by JK and YK. The first draft of the manuscript was written by JK and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements: None

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Tables

Table 1. The characteristics of patients enrolled in this study

n	61
Age (years)	57.4 ± 15.3
Men, n (%)	20 (33)
Child onset asthma, n (%)	7 (8)
GINA STEP, n (%)	
STEP 2	33 (54)
STEP 3	26 (43)
STEP 4	2 (3)
Duration of asthma (yr)	13.4 ± 7.0
Peripheral blood eosinophil count (%)	3.9 ± 3.4
IgE (IU/mL)	576.8 ± 1009.3
Serum perisotin (pg/mL)	79.3 ± 41.6
Pulmonary Function Test	
FVC(L)	3.2 ± 1.0
FEV_1 (L)	2.3 ± 0.8
FEV_1/ FVC (%)	71.3 ±10.0
FVC %predicted (%)	110.3 ± 19.3
FEV_1 %predicted (%)	98.9 ± 19.5
FEF_{50} (L)	2.1 ± 1.1
FEF_{25} (L)	0.6 ± 0.4
FEF_{50} %predicted (%)	49.6 ± 22.4
FEF_{25} %predicted (%)	32.1 ± 16.1

FEF_{50}: forced expired flow at 50% of vital capacity, FEF_{25}: forced expired flow at 25% of vital capacity, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, Global Initiative for Asthma: GINA

Data are presented as mean ± SD

Table 2. Correlations between serum NGAL level and clinical parameters

	r	p-value
Age	0.2706	***0.0349**
Duration of asthma	0.2673	***0.0373**
Peripheral blood eosinophil count	0.0934	0.4738
IgE	0.0620	0.6351
Serum periostin	0.0481	0.7131

* Significant, $p < 0.05$

Table 3. Multiple regression analysis of serum NGAL level

Variables	Parameter estimate	Standard error	Test stat	p-value
Age	0.2302	0.3729	0.617	0.5395
Men	-11.0026	11.4569	-0.960	0.3410
$FEV_1/FVC<70$	62.2653	17.3055	3.598	***0.0007**
Duration of asthma	-2.2923	1.1736	-1.953	0.0558

FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, * Significant, $p < 0.05$

Figures

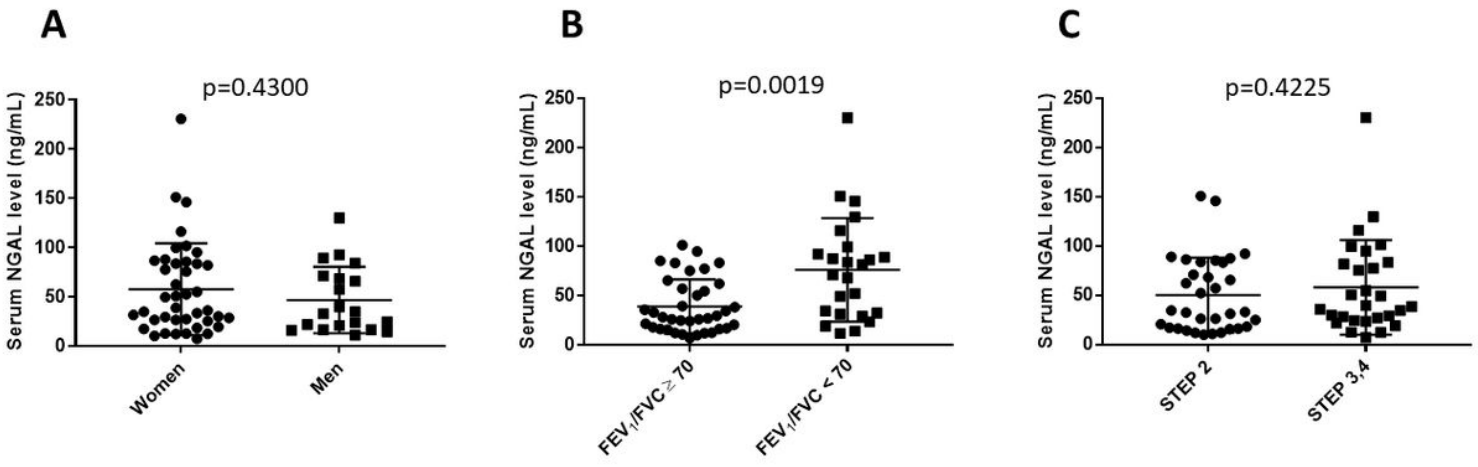

Figure 1

The association between serum NGAL levels and clinical parameters (A) There was no significant difference in serum NGAL levels between men and women (p=0.4300). (B) Serum NGAL levels in patients with obstructive ventilatory disorder were higher than those in patients without obstructive ventilatory disorder (p=0.0019). (C) There was no significant difference in serum NGAL levels between patients treated with GINA step 2 and those treated with GINA step 3 or 4 (p=0.4225).

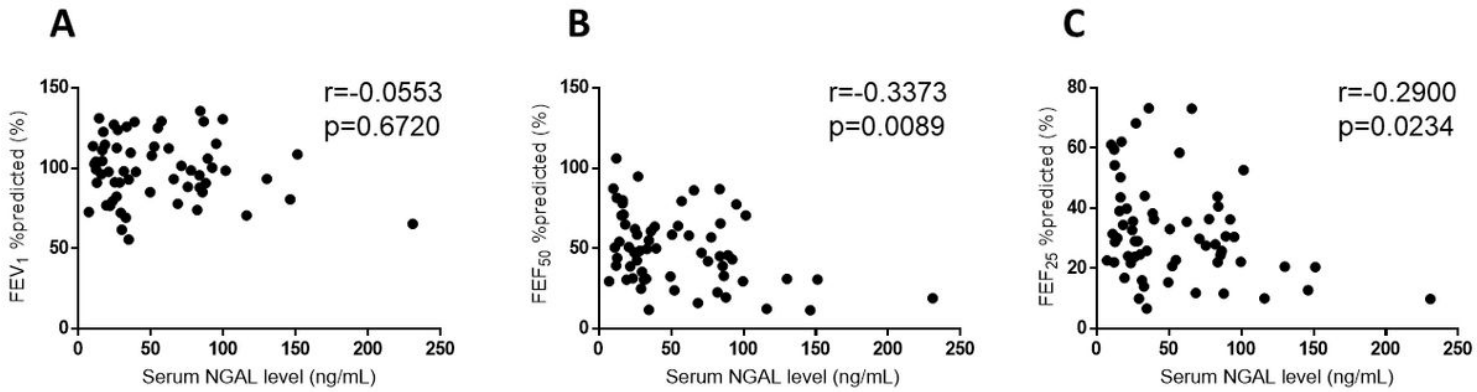

Figure 2

The association between serum NGAL levels and variables obtained by spirometry (A) Forced expiratory volume in 1 second (FEV1) %predicted was not correlated with serum NGAL levels. (B) Serum NGAL levels were negatively correlated with forced expired flow at 50% of vital capacity (FEF50) %predicted (r=-0.3373, p=0.0089). (C) Serum NGAL levels were negatively correlated with forced expired flow at 25% of vital capacity (FEF25) %predicted (r=-0.2900, p=0.0234).