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Relationship between serum arginase I and L-arginine or exhaled nitric oxide in asthma

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ABSTRACT

The relationship between serum arginase I and serum L-arginine or fractional exhaled nitric oxide (FENO) was evaluated cross-sectionally in asthmatic patients. No sex difference was observed in the serum mean levels of arginase I and L-arginine or FENO. Arginase I and FENO were higher in patients 60 or younger years than in those over 60 years. Asthmatic patients were divided into three groups: no steroid therapy, inhalation steroid therapy, and oral steroid therapy. Arginase I, FENO and high-sensitivity-C-reactive protein (hs-CRP) were significantly lower in the inhalation steroid therapy group than in the no steroid therapy group. Correlations were observed between arginase I and FENO, L-arginine, hs-CRP, WBC, and age, and also between FENO and IgE, WBC, and age. A logistic regression analysis revealed the positive association of arginase I with FENO, and the negative association of L-arginine. FENO was positively associated with arginase I and IgE. These results indicated that serum arginase I might influence serum levels of L-arginine and FENO, and that IgE might influence FENO in asthmatic patients.

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Introduction

The catabolism of L-arginine by arginase has been attracting attention as a modulator of endogenous NO production. Two distinct genetic isoforms, arginase I and II, are localized at different subcellular sites and function as urea cycle enzymes that catalyze the hydrolysis of L-arginine to urea and L-ornithine [1,2]. These enzymes down-regulate the generation of nitric oxide (NO) from nitric oxide synthase (NOS) by competing with the common enzyme substrate, L-arginine, which is metabolized to L-citrulline by NOS and to L-ornithine by arginase [2]. The induction of arginase in inflammatory tissues of the lung, intestines, and spinal cord has been shown to evoke the consumption of L-arginine, resulting in an abnormal pathophysiological state in animal tissue [3–5]. A large number of factors, including Th2 cytokines such as IL-4 and IL-13, growth factors, endotoxin, cAMP-elevating agents, oxygen tension, and reactive oxygen species (ROS), are known to be involved in the induction mechanisms of arginase in various rodent cells [6,7]. Although increased serum

levels of arginase I have been documented in several human studies such as those on asthma [8,9], sickle cell anemia [10], and colorectal cancer [11], the mechanisms underlying the induction of arginase currently remain unclear. We previously demonstrated the induction of arginase I in human asthmatic patients [12].

Low levels of L-arginine in asthmatic patients may contribute to high levels of arginase I [13]. However, no relationship has been observed between arginase activity and L-arginine in healthy controls or asthmatic patients [14]. In a healthy population, we found a relationship between serum arginase I and serum L-arginine [15]. After liver transplantation, an inconsistency was noted in the reduction of L-arginine by the release of arginase [16,17]. Therefore, an agreement has not yet been reached regarding the relationship between the serum level of arginase and that of L-arginine.

Fractional exhaled nitric oxide (FENO) is used in the diagnosis of asthma and other airway inflammatory diseases [18]. In healthy Caucasian adults, several factors such as age, gender, atopic constitution, smoking, and

diet have been shown to influence FENO [19–21]. In a healthy Japanese population, an inverse association was observed between L-arginine and FENO, while FENO was associated with IgE and NOx [15]. Therefore, it is a prerequisite to evaluate the relationship of elevated levels of arginase I with FENO and L-arginine in asthma.

Therefore, we herein investigate the relationship between arginase I and L-arginine or FENO in asthmatic patients.

Materials and methods

Study design

A cross-sectional study was designed to examine the relationship between arginase I and FENO or between arginase I and L-arginine. Thirty-three asthmatic patients were collected from a private clinic for respiratory medicine, 65 asthmatic patients were from the Departments of Respiratory Medicine of Kanazawa University Hospital and 80 asthmatic patients were from Kawasaki University Hospital from 2010 through 2013. We divided subgroups of asthma from 166 patients. Thirty-six were new patients with no steroid therapy until clinical status became stable, 119 patients received inhalation steroid therapy to maintain asthmatic status, and 11 patients received oral steroid therapy with poor therapy control. Twelve patients with a previous history of cancer, stroke, diabetes, ischemic heart disease, or liver disease, and for whom serum did not appear to be hemolytic, were ultimately neglected. The Ethics Committee of Okayama University approved this study as number 1128, 1130, and 1131, and all subjects gave informed consent.

Measurement of clinical parameters for whole blood and serum

Blood samples were collected after overnight fasting. Sera were separated and preserved at -80°C until analyzed. Whole blood and separated sera were measured for hematological parameters (WBC) using automated XE-2100 (Sysmex, Kobe city, Japan). Serum high-sensitivity-C-reactive protein (hs-CRP) was measured by a highly sensitive CRP assay (Behring Latex-Enhanced using the Behring Nephelometer BN-100; Behring Diagnostics, Westwood, MA). Arginase I and IgE were determined using ELISA kits from Bethyl Laboratories (Montgomery, TX) and Hycult Biotechnology b.v. UDEN, respectively. Information on lifestyle factors including cigarette smoking, previous medical history, and present steroid medication was obtained using self-reported questionnaires or clinical records.

Measurement of FENO

FENO was measured using a portable electrochemical analyzer (Niox Mino, Aerocine AB, Sweden). According to international recommendations this device measures FENO during a 10-s exhalation with a constant flow of 50 mL s^{-1} . All measurements were performed in duplicate, all within a 10% deviation, and the mean concentration in parts per billion (ppb) was registered.

Measurement of serum NOx

Serum NOx ($\text{NO}_2^- + \text{NO}_3^-$) levels were determined with a NO analyzer (model-280i NOA with the Purge Vessel; Sievers, Boulder, CO) to evaluate the relationship between arginase I and generation of NO [22]. Serum nitrate was changed to nitrite by nitrate reductase (Sigma-Aldrich, St. Louis, MO) after an incubation at room temperature for 30 min. Nitrite was further reduced to NO in the Purge Vessel containing the reducing agent potassium iodide in acetic acid, and the NO generated was transported to the NO analyzer using the ozone-chemiluminescence method.

Measurement of serum L-arginine

Serum L-arginine was measured using a HPLC system (HITACHI, Tokyo, Japan) with slight modifications [23]. L-arginine was eluted from serum and supplemented with $5\text{ }\mu\text{M}$ monomethylarginine (MMA) as an internal standard using Oasis MCX solid phase-extraction (SPE) cartridges (Waters, Milford, MA) conditioned with 2 mL of methanol/water/ammonia solution (50:40:10, vol/vol/vol) and phosphate-buffered saline (PBS). Serum samples containing $5\text{ }\mu\text{M}$ MMA were dissolved in PBS and loaded onto an equilibrated SPE column. The column was constitutively washed with 0.1 N HCl (2 mL) and methanol (2 mL). The fraction containing L-arginine was eluted with 1 mL of methanol/water/ammonia solution (50:40:10, vol/vol/vol) and dried in a vacuum centrifuge. After the drying process, the residue was reconstituted with water. The samples reconstituted with water for L-arginine were mixed with an equal amount of derivatizing agent (5 mg/mL ortho-phthalaldehyde, 10% methanol, and 0.5% 3-mercaptopropionic acid in 200 mM borate buffer, pH 8.5), and the reaction was allowed to occur at room temperature for 30 min. The samples for L-arginine were introduced into the fluorescence HPLC system using a TSKgel ODS-100V column ($4.6 \times 250\text{ mm}$, $5\text{ }\mu\text{m}$, Tosoh, Yamaguchi, Japan) with the mobile phase consisting of 9% acetonitrile in acetate buffer (pH 6.3) at a flow rate of 1.5 mL/min . The detection of each amino acid was performed using excitation

and emission wavelengths of 340 and 455 nm, respectively.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 5.0c for Mac (GraphPad Software, Inc., San Diego, CA) and PASW Statistics 18 for Mac. Results are expressed as means $\pm$ SEM. Group comparisons for continuous variables were performed by an unpaired *t*-test or Mann–Whitney *U* test if the data were not normally distributed. Difference in clinical parameters among three groups (steroid free group, inhalation steroid group and oral steroid group) were analyzed age-adjusted ANCOVA. Spearman's correlation was used for correlation analyses. The unpaired *t*-test and a multiple regression analysis were performed using values transformed into the log₁₀ format. The chi-squared test was used to compare the proportions of sex and age. After conducting multicollinearity diagnostics among the independent variables, we performed a binomial logistic regression analysis to evaluate the independent relationships between arginase I, FeNO, and various clinical parameters for all asthmatic patients and those receiving inhalation steroid therapy by expressing of ORs for tertiles range of explanatory variables. Adjustment was performed by deletion of an objective variable from total variables such as sex, age, hs-CRP, FENO, WBC, arginase I, L-arginine, NOx, IgE, cigarette smoking habit, and corticosteroid therapy. Tests for a linear trend across the

ORs of arginase I tertiles, L-arginine tertiles, hs-CRP tertiles, FENO tertiles, and IgE tertiles were conducted by means of an orthogonal polynomial contrast. A probability value of $p < 0.05$ was considered to be significant.

Results

Characteristics of subjects by several clinical parameters

The characteristics of the subjects by several clinical parameters in this study are presented in Tables 1 and 2. The average age was 57.0 years. The serum concentrations of arginase I and L-arginine in asthmatic patients ($n = 166$) were 55.8 ± 6.3 ng/ml and 116.6 ± 3.4 μ M, respectively. The mean value of FENO in asthmatic patients was 50.7 ± 3.6 ppb. Sex differences were not observed in these clinical parameters. However, arginase I, FENO, IgE, and WBC were higher in patients younger than 60 years than in those older than 61 years. NOx and hs-CRP were higher in patients older than 61 years than in those younger than 60 years (Table 1).

When clinical parameters were examined following the division of patients into three groups based on corticosteroid therapy (steroid free group, inhalation steroid group, and oral steroid group), arginase I, FENO, and hs-CRP were significantly lower in the inhalation steroid therapy group than in the no steroid therapy group (Table 2).

Table 1. Characteristics of subjects by several clinical parameters.

Variable	All Mean $\pm$ SEM ($n = 166$)	Male Mean $\pm$ SEM ($n = 70$)	Female Mean $\pm$ SEM ($n = 96$)	<i>p</i>	Age <60 Mean $\pm$ SEM ($n = 82$)	Age ≥ 61 Mean $\pm$ SEM ($n = 84$)	<i>p</i>
Age	57.0 $\pm$ 1.4	55.8 $\pm$ 2.1	57.7 $\pm$ 1.8	0.420			
Sex (M/F)					40/42	30/54	0.008
Arginase I (ng/mL)	55.8 $\pm$ 6.3	54.7 $\pm$ 7.6	56.6 $\pm$ 9.4	0.938	70.9 $\pm$ 11.5	40.3 $\pm$ 4.2	0.003
L-arginine (μ M)	116.6 $\pm$ 3.4	118.4 $\pm$ 4.1	114.2 $\pm$ 5.2	0.132	115.1 $\pm$ 5.0	116.7 $\pm$ 4.9	0.711
FENO (ppb)	50.7 $\pm$ 3.6 (151)	56.8 $\pm$ 6.5 (65)	46.2 $\pm$ 3.9 (86)	0.318	65.7 $\pm$ 5.6 (76)	35.6 $\pm$ 3.9 (75)	<0.001
NOx (jxM)	49.4 $\pm$ 3.3	44.6 $\pm$ 5.1	53.0 $\pm$ 4.4	0.069	42.0 $\pm$ 4.3	57.0 $\pm$ 4.4	0.003
IgE (IU/mL)	184.2 $\pm$ 17.9	173.6 $\pm$ 24.7	191.4 $\pm$ 25.0	0.921	229.7 $\pm$ 30.6	136.8 $\pm$ 16.2	0.023
hs-CRP (mg/dL)	1.6 $\pm$ 0.3	1.7 $\pm$ 0.5	1.6 $\pm$ 0.3	0.581	1.2 $\pm$ 0.2	2.0 $\pm$ 0.5	0.029
WBC (cell/mL)	5696 $\pm$ 58.4 (142)	6449 $\pm$ 289.1 (60)	6549 $\pm$ 230.3 (82)	0.654	6974 $\pm$ 264.6 (69)	6065 $\pm$ 235.3 (73)	0.009

Table 2. Characteristics of subjects by several clinical parameters.

Variable	Steroid free Mean $\pm$ SEM ($n = 36$)	Inhalation steroid Mean $\pm$ SEM ($n = 119$)	Oral steroid Mean $\pm$ SEM ($n = 11$)	<i>p</i>
Age	50.5 $\pm$ 3.2	58.9 $\pm$ 1.6*	57.6 $\pm$ 4.4	0.047
Sex (M/F)	0.51 $\pm$ 0.08	0.63 $\pm$ 0.05	0.27 $\pm$ 0.15	0.046
Arginase I (ng/mL)	61.3 $\pm$ 13.7	53.4 $\pm$ 7.4**	64.3 $\pm$ 24.4	0.006
L-arginine (μ M)	127.3 $\pm$ 7.5	113.1 $\pm$ 4.1	119.1 $\pm$ 13.3	0.246
FENO (ppb)	86.9 $\pm$ 7.4 (29)	41.5 $\pm$ 3.7 (113)***	50.2 $\pm$ 13.0 (9)*	<0.001
NOx (μ M)	54.9 $\pm$ 7.1	46.9 $\pm$ 3.9	58.2 $\pm$ 12.6	0.246
IgE (IU/mL)	146.1 $\pm$ 38.2	197.5 $\pm$ 20.7	163.5 $\pm$ 67.1	0.477
hs-CRP (mg/dL)	3.1 $\pm$ 0.63	1.0 $\pm$ 0.33*	3.1 $\pm$ 1.1	0.006
WBC (cell/mL)	6727 $\pm$ 373 (31)	6269 $\pm$ 205 (101)	8211 $\pm$ 650 (10)#	0.016

Values except for age represents age adjusted mean $\pm$ SEM by ANCOVA among steroid free group, inhalation steroid group and oral steroid group. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus steroid free group and # $p < 0.05$ versus inhalation steroid group.

Table 3. Correlation of arginase I and FENO with clinical parameters in asthma patients.

Variables	Arginase I				FENO			
	<i>r</i> (All)	<i>r</i> (Steroid free)	<i>r</i> (Inhalation sterio)	<i>r</i> (Oral steroid)	<i>r</i> (All)	<i>r</i> (Steroid free)	<i>r</i> (Inhalation sterio)	<i>r</i> (Oral steroid)
Age	−0.206**	−0.166	−0.189*	−0.032	−0.324***	−0.256	−0.226*	−0.544
Sex (M/F)	0.006	0.219	−0.060	0.323	−0.082	−0.082	−0.090	0.207
L-arginine	−0.251***	−0.141	−0.310**	−0.518	0.138	0.154	−0.004	0.417
FENO	0.234**	0.028	0.169	0.117				
NOx	0.124	0.003	0.084	0.355	0.103	0.069	0.102	−0.100
IgE	−0.113	−0.102	−0.153	0.291	0.304***	0.302	0.302**	0.933***
hs-CRP	0.191*	0.553**	0.055	0.437	−0.018	−0.313	0.025	−0.142
WBC	0.259**	0.624**	0.127	0.600	0.249**	0.311	0.207*	−0.544

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Correlation analysis between arginase I, FENO, and clinical variables

Spearman's correlation coefficients of arginase I and FENO with several clinical parameters were presented by stratifying asthmatic patients based on steroid therapy in Table 3. Serum levels of arginase I positively correlated with FENO, hs-CRP, and WBC, and negatively correlated with L-arginine and age. Negative correlations of arginase I with age and L-arginine were dependent on asthma patients of inhalation steroid therapy. Positive correlations of arginase I with hs-CRP and WBC were dependent on asthmatic patients of no steroid therapy. FENO positively correlated with IgE and WBC, and negatively correlated with age, and these correlations were dependent on asthmatic patients of inhalation steroid therapy.

The correlation of arginase I with L-arginine and FENO, and that of FENO with IgE are presented as scatter diagrams in Figure 1. Data were analyzed by Spearman's correlation after the log-transformation of variables.

Logistic regression analyses for arginase I and FENO with clinical variables

The results of the logistic regression analysis showed the reduced odds ratio (OR) of arginase I for L-arginine in the range of Q2 (OR = 0.28 [95% CI, 0.09–0.93]) to Q3 (OR = 0.23 [95%CI, 0.07–0.74]) (p for trend 0.014) and the increased odds ratio of arginase I for FENO in the range of Q2 (OR = 7.09 [95% CI, 1.96–25.67]) and Q3 (OR = 7.23 [95% CI, 1.85–28.30]) (p for trend 0.005) in Table 4. By stratifying asthmatic patients based on inhalation steroid therapy, the relationship for arginase I with L-arginine was observed as OR in Q3 (OR = 0.20 [95% CI, 0.06–0.71]) (p for trend 0.013) and with FENO as OR in Q3 (OR = 5.35 [95% CI, 1.38–20.76]) (p for trend 0.015).

Regarding the OR for FENO, positive associations were shown for arginase I in Q3 (OR = 6.35 [95% CI, 1.63–24.79]) (p for trend 0.008) and for IgE in Q3 (OR = 4.96 [95% CI, 1.55–15.84]) in Table 5. By stratifying asthmatic patients based on inhalation steroid therapy, the ORs for FENO according to arginase I and IgE were

increased in Q3 (OR = 5.32 [95% CI, 1.33–21.29]) (p for trend 0.018) and Q3 (OR = 6.10 [95% CI, 1.82–20.53]) (p for trend 0.003).

Discussion

A large number of studies on arginase have used activity assays, and four previous studies reported contradictory findings for the levels of serum arginase activities in asthmatic patients [8,9,13,14]. High levels of serum arginase I and its correlation with hs-CRP were shown in asthmatic patients using ELISA [12]. However, the relationship between arginase activity and L-arginine levels is not clear. No correlation was found between arginase activity and L-arginine in healthy controls or asthmatic patients [14]. We previously demonstrated that arginase I was negatively associated with L-arginine and 3-nitrotyrosine in healthy individuals [15]. Decreases in L-arginine levels by arginase I may contribute to the generation of 3-nitrotyrosine, an oxidative stress biomarker, due to the uncoupling of NOS. However, although arginase I was inversely associated with L-arginine in asthmatic patients in the present study, the generation of 3-nitrotyrosine due to the uncoupling of NOS was not confirmed. The up-regulation of arginase I in a mouse asthma model has been suggested to reduce the generation of NO in order to enlarge bronchial smooth muscle through the consumption of L-arginine for NOS [3–5]. In sickle cell anemia, arginase I released from hemolytic red blood cells consumed L-arginine and resulted in the onset of asthma and pulmonary hypertension due to reductions in NO levels [10]. Therefore, the generation of NO in asthmatic lungs may be reduced due to decreased levels of L-arginine.

On the other hand, the up-regulation of FENO is commonly recognized in asthma in association with airway inflammation [18]. However, the mechanism responsible for the up-regulation of FENO in asthmatic patients has not yet been conclusively explained, as described above, because NO in the lung tissue of asthmatic patients is insufficient due to the consumption of L-arginine by

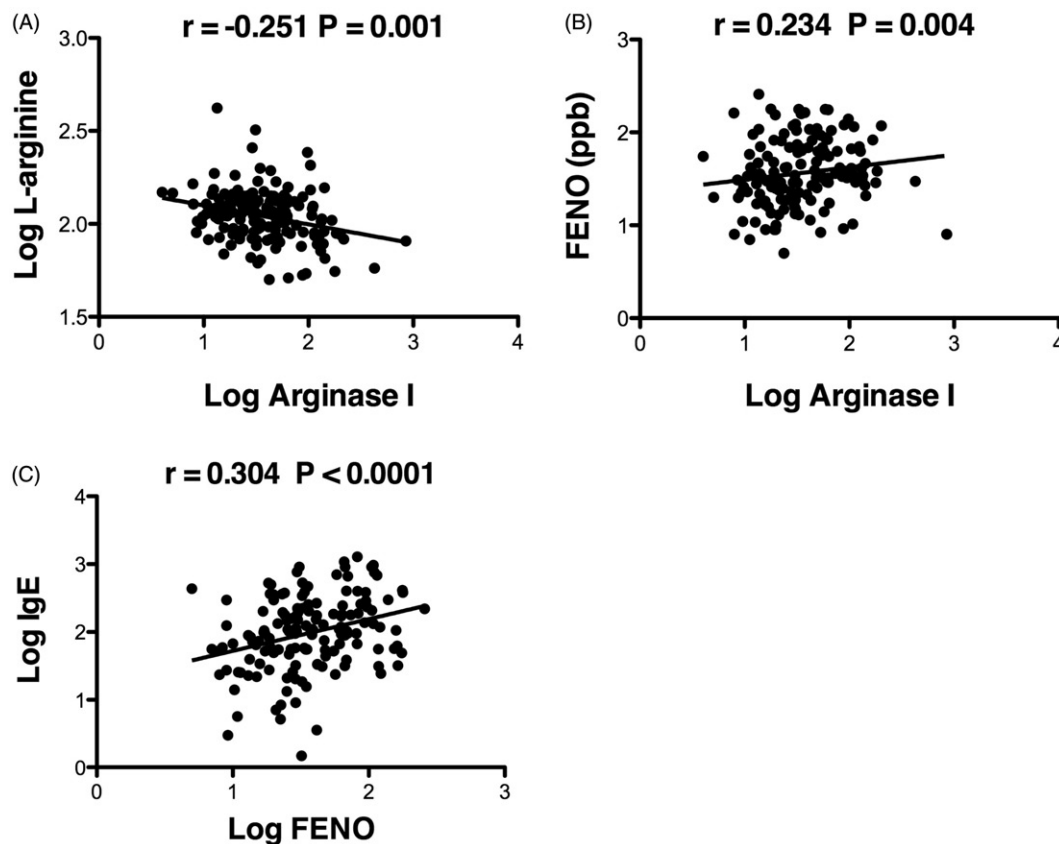


Figure 1. Spearman's correlation of log-transformed values. Serum arginase I was significantly correlated with L-arginine (A) and FENO (B), and FENO was significantly correlated with IgE (C).

Table 4. Odds for arginase I according to L-arginine, FENO, hs-CRP, and age.

Population group	Explanatory variable	Q1	Q2	Q3	<i>p</i> for trend
All ^a	L-arginine	1	0.28 (0.09–0.93)	0.23 (0.07–0.74)	0.014
	hs-CRP	1	0.86 (0.27–2.75)	3.05 (0.95–9.84)	0.062
	FENO	1	7.09 (1.96–25.67)	7.23 (1.85–28.30)	0.005
Inhalation steroid ^b	L-arginine	1	0.41 (0.11–1.45)	0.20 (0.06–0.71)	0.013
	hs-CRP	1	0.68 (0.19–2.44)	1.67 (0.46–6.01)	0.435
	FENO	1	1.52 (0.42–5.50)	5.35 (1.38–20.76)	0.015

Parentheses represents 95% confidence interval and bold values mean statistical significance compared to reference.

^aOdds for arginase I according to tertile of a selected explanatory variable omitting a variable from age, sex, hs-CRP, FENO, WBC, L-arginine, NOx, IgE, cigarette smoking and corticosteroid therapy for the adjustment.

^bOdds for arginase I according to tertile of a selected explanatory variable omitting a variable from age, sex, hs-CRP, FENO, WBC, L-arginine, NOx, IgE, and cigarette smoking for the adjustment.

up-regulated arginase I [4,5,24]. FENO in healthy individuals may be associated with several factors such as age, gender, atopic constitution, smoking, and diet [19–21]. In a healthy Japanese population, an inverse association between FENO and L-arginine and a positive association between FENO and arginase I were observed in addition to FENO being associated with IgE and NOx [15]. In asthmatic patients in the present study, a positive association was observed between FENO and arginase I in addition to the inverse association between arginase I and L-arginine. Therefore, arginase I may down-regulate L-arginine and an unknown common mechanism for the up-regulation of FENO and arginase I may exist in healthy individuals and asthmatic patients.

FENO is associated with blood eosinophilia, but only in patients with atopic asthma [25]. Several studies showed that FENO might be more closely associated with atopy than with asthma [26,27]. A previous study on healthy individuals reported a positive association between FENO and IgE [13]. In asthmatic airways, mast cells play a role in allergic airway inflammation. They possess IgE receptors. In human culture mast cells or mouse mast cells, the addition of IgE has been shown to induce the generation of NO from NOS2 and NOS3 [29,30]. Therefore, the independent association between FENO and IgE in this study suggests that FENO may be generated in mast cells by the reaction between IgE and the IgE receptor.

Table 5. Odds for FENO according to arginase I, IgE, and age.

Population group	Explanatory variable	Q1	Q2	Q3	<i>p</i> for trend
All ^a	Arginase I	1	2.26 (0.71–7.23)	6.35 (1.63–24.79)	0.008
	IgE	1	1.68 (0.55–5.10)	4.96 (1.55–15.84)	0.007
Inhalation steroid ^b	Arginase I	1	1.11 (0.34–3.67)	5.32 (1.33–21.29)	0.018
	IgE	1	1.38 (0.43–4.50)	6.10 (1.82–20.52)	0.003

Parentheses represents 95% confidence interval and bold values mean statistical significance compared to reference.

^aOdds for FENO according to tertile of a selected explanatory variable omitting a variable from age, sex, hs-CRP, WBC, arginase I, L-arginine, NOx, IgE, cigarette smoking and corticosteroid therapy for the adjustment.

^bOdds for FENO according to tertile of a selected explanatory variable omitting a variable from age, sex, hs-CRP, WBC, arginase I, L-arginine, NOx, IgE, and cigarette smoking for the adjustment.

FENO has been used clinically for the diagnosis and management of asthma because its correlation with lung function, sputum eosinophils and methacholine responsiveness [30–32]. However, when the dose of inhalation steroid increased and FENO reduced due to inhibitory action of corticosteroid, FEV1 was not changed. Therefore, it is said that FENO is not useful to predict the exacerbation. In this study, arginase I showed almost similar changes with FENO. Up-regulated arginase I may be derived from inflammatory lung of asthma. Therefore, arginase I may be a biomarker for the supportive diagnosis of asthma.

CRP, a well-known inflammatory marker, is easily measured for evaluations of systemic inflammation [28]. Serum hs-CRP was recently found to be involved in cardiovascular disease and diabetes mellitus with low-grade systemic inflammation [29,33,34]. Moreover, serum levels of hs-CRP were shown to be increased in asthmatic patients and correlated with respiratory symptoms [35], severe asthma [36], and airway inflammation [37]. In a previous study, serum hs-CRP levels were significantly higher in asthmatic patients than in healthy controls, and serum levels of arginase I correlated with hs-CRP in asthmatic patients [12]. Moreover, serum protein levels of arginase I were associated with hs-CRP in 721 healthy individuals [38]. Regarding asthmatic patients in the present study, a stronger correlation was observed between arginase I and hs-CRP in asthmatic patients receiving no steroid therapy than in those receiving inhalation steroid therapy (Table 3). The disappearance of the association between arginase I and hs-CRP by logistic regression analysis (Table 4) may be due to the small number of asthmatic patients with no steroid therapy group because when hs-CRP was divided to four categories, a significant association between arginase I and hs-CRP was shown.

Although the results of the present study are significant, there were several limitations. The sample size was small. Furthermore, it was not possible to determine causal relationships because this study was cross-sectional.

In conclusion, the negative association of serum arginase I with L-arginine suggests the regulation of serum

L-arginine levels by arginase I, while the positive association of FENO with arginase I indicates the possible existence of a common inducing factor for FENO and arginase I. Moreover, arginase I may be one of the therapeutic biomarkers in asthma. However, further studies on more many asthmatic patients are needed in order to confirm this.

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Disclosure statement

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