

BIOMARKERS

sICAM-1 and TNF- α in Asthma and Rhinitis: Relationship with the Presence of Atopy

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Background. A genetically determined overproduction of specific immunoglobulin E (IgE) underlies many diseases like asthma or allergic rhinitis. IgE as well as tumor necrosis factor- α (TNF- α), and intercellular adhesion molecule-1 (ICAM-1) play a critical role in the induction and maintenance of inflammation. While the correlation between IgE and atopy is inseparable, little is known about the correlation of atopy with markers of inflammation. **Objective.** We investigated the relationship between the serum concentrations of TNF- α , soluble ICAM-1 (sICAM-1), and the presence of atopy in patients with persistent rhinitis or asthma. **Methods.** Serum concentrations of sICAM-1, TNF- α , and total IgE were investigated in 64 adults with persistent allergic rhinitis, 17 subjects with nonatopic rhinitis, 90 patients with asthma, and 21 healthy individuals. Atopy was diagnosed on the basis of positive family history, skin prick tests, and serum IgE concentration. **Results.** Total IgE concentration was significantly higher in patients with atopic rhinitis or asthma when compared with nonatopic patients and healthy individuals and was the highest in patients suffering from severe atopic asthma who were not treated with systemic glucocorticosteroids. Although there were marked alterations in IgE in atopic and nonatopic patients, there were no significant differences between atopic and corresponding groups of nonatopic rhinitic and asthmatic patients in sICAM-1 and TNF- α concentrations. (sICAM-1 in rhinitis: atopic vs. nonatopic patients: 224.02 and 221.08 ng/ml, respectively, $p > .05$; in mild/moderate asthma: atopic vs. nonatopic: 306.22 and 326.39 ng/ml, respectively, $p > .05$; severe asthma without oral corticosteroids therapy: atopic vs. nonatopic: 418.03 and 468.09 ng/ml, respectively, $p > .05$; and severe asthma with oral corticosteroids therapy: atopic vs. nonatopic: 320.66 and 308.09 ng/ml, respectively, $p > .05$). **Conclusions.** Concentrations of sICAM-1 and TNF- α are significantly higher in patients with asthma compared with those observed in patients with rhinitis, but they are independent of the presence of atopy.

Keywords allergic inflammation, allergic rhinitis, atopy, inflammation, nonatopic rhinitis

INTRODUCTION

Immunoglobulin E (IgE) plays a critical role in atopic diseases such as bronchial asthma and allergic rhinitis. It is present in the early phase and also induces the chronic phase of allergic inflammation (1–4). Antigen-induced cross-linking of the superficial IgE activates mast cells through high-affinity IgE receptor (Fc ϵ RI), resulting in the synthesis and release of cytokines and mediators and results in the airway bronchoconstriction, mucus production, edema, and the recruitment of inflammatory cells. Furthermore, chronic allergic inflammation is driven by eosinophil infiltration and is dependent on the production of Th2-type cytokines such as IL-4 and IL-5 (5). Leukocyte–endothelial adhesion molecules are critical in leukocyte accumulation. They are involved in the initial stages of recruitment and migration of cells from the circulation to sites of inflammation. Intercellular adhesion molecule-1 (ICAM-1) plays a prominent role in allergic rhinitis and asthma-mediating T-cell interactions, signal transduction, modulating cell activation, proliferation, and cytokine production (6). The expression of ICAM-1

is upregulated by the tumor necrosis factor- α (TNF- α) which is a pro-inflammatory cytokine produced by activated cells in the area of inflammation (7, 8). TNF- α augments airway inflammation, upregulates adhesion molecules, induces the expression of airway epithelial cell genes including cytokines and chemokines, increases the adhesion of activated eosinophils to epithelial cells, and promotes neutrophil chemotaxis (9).

Since TNF- α and ICAM-1 play a crucial role in allergic inflammation and their upregulation and release from human lung tissue may be increased by IgE receptor activation (10), we wanted to examine the correlation between overproduction of specific IgE and concentrations of soluble ICAM-1 (sICAM-1) and TNF- α in subjects with atopic and nonatopic asthma as well as in subjects with persistent atopic and nonatopic rhinitis. Additionally, we wanted to check whether atopic and nonatopic asthma are distinct features of the disease considering their clinical characteristics and the inflammation background.

MATERIALS AND METHODS

Study Population

Patients with Persistent Allergic Rhinitis (Group A). Sixty-four subjects (36 females, 28 males) with persistent

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allergic rhinitis were included in the study. The inclusion criteria are as follows: a minimum 2-year history of persistent allergic rhinitis classified according to Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines (11), total nasal symptom score (TNSS) of at least 6, positive skin prick tests, and specific serum IgE for *Dermatophagoides farinae* and/or *Dermatophagoides pteronyssinus*. Drug-induced rhinitis and nasal polyps were exclusion criteria.

Patients with Nonatopic Rhinitis (Group B). Seventeen subjects (13 females, 4 males) with persistent nonatopic rhinitis were examined. We included only patients with a minimum 2-year history of idiopathic or drug-induced rhinitis, negative atopic history, negative results in skin prick tests, and normal serum IgE concentrations. All rhinitic patients could not be asthmatics nor have nasal septum deviations. They could not use topical or oral corticosteroids, leukotriene modifiers, or antihistamines 4 weeks preceding the study.

Patients with Persistent Asthma. Ninety subjects (67 females, 23 males) with at least a 1-year history of persistent asthma diagnosed on the basis of the global strategy for asthma management and prevention recommendations Global Initiative for Asthma (GINA) (12) were included in the study. The inclusion criteria are as follows: positive result of spirometric reversibility or metacholine challenge test, stable dose of anti-asthmatic medications in the last 6 weeks, and controlled disease 4 weeks prior to the study, according to the GINA (12) recommendations. Patients were excluded if they had asthma exacerbation 4 weeks preceding the study.

The exclusion criteria for all participants included a history of recurrent infections of the respiratory tract and acute respiratory infection 4 weeks preceding the examination, chronic sinusitis, current smoking, significant renal, hepatic, pulmonary, or cardiovascular disease, specific immunotherapy, pregnancy, and neoplastic disease.

Asthmatic patients were divided into six groups according to the atopic history, asthma severity, and treatment as follows:

Group 1—atopic patients with mild or moderate asthma ($n = 36$)

Group 2—nonatopic patients with mild or moderate asthma ($n = 14$)

Group 3—atopic patients with severe asthma without oral corticosteroids therapy ($n = 19$)

Group 4—nonatopic patients with severe asthma without oral corticosteroids therapy ($n = 4$)

Group 5—atopic patients with severe asthma with oral corticosteroids therapy ($n = 8$)

Group 6—nonatopic patients with severe asthma with oral corticosteroids therapy ($n = 9$)

Twenty-one healthy subjects (12 females, 9 males) were included as a control with negative atopic history, negative results in skin prick tests, and normal serum IgE concentrations (Tables 1 and 2).

Study Design

After the written consent form was obtained, a detailed medical history was taken and a complete physical examination was done; skin prick tests and spirometry were performed. Then peak expiratory flow (PEF) meters and symptom diaries were handed out and the patients were asked to monitor nasal or asthmatic symptoms for the following 4 weeks. At visit 1 the eligibility criteria were evaluated, skin prick tests were carried out, laryngological examination was carried out, and blood samples were taken from all subjects. The severity of asthma was classified according to the GINA report (12), and the severity of rhinitis was classified according to the ARIA report (11) as “mild” or “moderate-severe.” The study protocol was approved by the Local Ethical Committee.

Total Symptom Score

Patients reported their total symptom score (TSS) using a 4-point scale (0—none, 1—mild symptom, 2—moderate, 3—severe). The TSS was the sum of four nasal symptom scores (rhinorrhea, nasal itching, sneezing, congestion) and four ocular symptom scores (itchy, burning, tearing, watering eyes). Results were expressed as TSS, TNSS, and total eyes symptom score (Table 2).

TABLE 1.—Characteristics of asthmatic patients and healthy control.

	Patients with atopic asthma	Patients with nonatopic asthma	Healthy control
Number of patients	63	27	21
Age (years)	43.39 $\pm$ 2.02	50.85 $\pm$ 2.49	29.76 $\pm$ 1.9
Sex ratio (M/F)	25/38	6/21	9/12
Family history of asthma/allergy	24 (38.1%)	12 (44.4%)	3 (14.3%)
Reported allergic rhinitis	47 (74.6%)	0	0
Reported ever having allergic dermatitis	2 (3.18%)	0	0
Reported ever having eczema (food allergy)	16 (25.39%)	0	0
History of asthma (years)	13.13 $\pm$ 1.41	15.19 $\pm$ 1.85	0
FEV ₁ (percent predicted)	82.14 $\pm$ 2.57	78.19 $\pm$ 3.3*	97.6 $\pm$ 2.3**
Asthma symptom score	3.83 $\pm$ 0.4	4.81 $\pm$ 0.57	0

Notes: Data are expressed as mean value $\pm$ SEM. FEV₁, forced expiratory volume in 1 s.

P-values: * $p < .01$ (vs. patients with atopic asthma), ** $p < .01$ (vs. patients with atopic and nonatopic asthma).

TABLE 2.—Characteristics of patients with rhinitis and healthy control.

	Allergic rhinitis	Nonatopic rhinitis	Healthy control
Number of patients	64	17	21
Age (years)	28.26 ± 1.23	31.89 ± 3.54	29.76 ± 1.9
Sex ratio (M/F)	49/15	4/13*	9/12
Family history of allergy (n)	12 (18.75 %)	3 (17.65 %)	3 (14.3%)
Reported ever having eczema (food allergy) (n)	3 (4.69 %)	0	0
Rhinitis duration	8.59 ± 0.78	7.24 ± 1.48	0
Total symptom score (max. 24 points)	8.31 ± 0.31	8.0 ± 0.66	2.65 ± 0.27**
Rhinorrhea score	2.07 ± 0.11	2.41 ± 0.17	0.7 ± 0.12**
Itching score	1.29 ± 0.13	0.53 ± 0.21*	0.29 ± 0.1**
Congestion score	2.04 ± 0.1	2 ± 0.24	0.66 ± 0.11**
Sneezing score	1.89 ± 0.09	2 ± 0.24	0.63 ± 0.12**
Total eyes symptom score (max. 12 points)	1.06 ± 0.13	1.06 ± 0.31	0.35 ± 0.11**
Total nasal symptom score (TNSS) (max. 12 points)	7.05 ± 0.27	6.81 ± 0.65	2.29 ± 0.24**
Laryngological score (max. 12 points)	4.9 ± 0.16	4.65 ± 0.24	2.11 ± 0.24**
Rhinitis severity: mild/moderate–severe (n)	29/35	3/14	0

Notes: Data are expressed as mean value ± SEM.

P-values: * $p < .05$ (vs. allergic rhinitis group), ** $p < .01$ (vs. allergic and nonatopic rhinitis groups).

Asthma Symptom Score

Patients with persistent asthma reported their wheeze/dyspnea, cough, activity, and sleep using a 4-point scale: wheeze/dyspnea (0—none, 1—some, 2—medium, 3—severe); cough (0—none, 1—occasional, 2—frequent, 3—continuous); activity (0—normal, 1—can run short distance or climb three flights of stairs, 2—can walk only, 3—missed school/work or stayed indoors); sleep (0—fine, 1—slept well, slight wheeze, or cough, 2—awake 2–3 times, wheeze, and/or cough, 3—bad night, awake all the time). Total daily asthma symptom score ranged from 0 to 12.

IgE and Skin Prick Tests

Atopy was defined by positive history, positive skin prick test results, and/or high concentration of total serum IgE > 100 IU/ml.

Skin Prick Tests

Skin prick tests with the standard set of aeroallergens (Eastern tree mix, tree mix, weed mix, *D. pteronyssinus* and *D. farinae*, cat, dog, ribwort, nettle, *Alternaria*, *Aspergillus*; Allergopharma J. Ganzer KG, Reinbek, Germany) were performed for each patient with histamine (10 mg/ml) as a positive control and diluent as a negative control. Results were assessed as positive when the mean wheal diameter (assessed as a sum of the largest diameter and its perpendicular measurement) was greater than 3 mm.

Determination of Total Serum IgE Concentrations

Total serum IgE levels were assessed by sandwich ELISA (ELISA kit, Allergopharma, Warsaw, Poland) according to the manufacturer's instructions. Minimum detectable concentration was 1 IU/ml.

Determination of Serum sICAM-1 and TNF- α

The serum concentrations of sICAM-1 and TNF- α were examined by sandwich ELISA (ELISA kit, R&D Systems, Warsaw, Poland) according to the manufacturer's instructions. Minimum detectable concentrations were 0.35 ng/ml for sICAM-1 and 0.11 pg/ml for TNF- α , respectively.

Anterior Rhinoscopy

Evaluation of nasal cavity, morphology, and patency was performed using an optical method. The chondrocostal structure was assessed according to the method of Gustafson and Kern with morphology of the nasal mucous membrane being described with respect to color, edema, redness, and discharge using 0- to 3-point scale (0—none, 1—mild symptom, 2—moderate, 3—severe).

Methacholine Challenge Test

Provocation tests were performed according to the method described by Cockcroft et al. (13) using successively increased concentrations of methacholine (from 0.03 to 16 mg/ml) inhaled from DeVilbiss 646 nebulizer (tidal breathing, 2 min, with the operating airflow rate of 6 l/min and a mean output of 0.26 ml/min) (DeVilbiss Healthcare, Somerset, PA, USA). The test was withheld at a concentration of methacholine that caused a decrease in forced expiratory volume in 1 s (FEV₁) of 20% or greater than that caused by phosphate buffered saline (PBS) (provocative concentration). The methacholine concentration (PC20) that provoked a 20% fall in FEV₁ was calculated by logarithmic interpolation. Subjects with PC20 < 8 mg/ml were considered to have bronchial hyperresponsiveness (BHR).

Spirometry

Spirometry was performed with a computer-assisted spirometer (Lung Test 1000, MES Dymek, D'browski SA, Krakow, Poland) according to standardized

guidelines (11). Values were expressed as percentage of predicted values.

PEF Evaluation

PEFs were monitored daily in the morning and in the evening on all asthmatic patients in a 4-week screening period using a commercial PEF meter (Datospir 10, Sibelmed, Spain). Values were recorded in patients' diaries.

Statistical Analysis

All data were presented as mean $\pm$ SEM. Normality of distributions was assessed using the Shapiro–Wilk tests. A parametric methods comparison between groups was done using Student's *t*-test. Nonparametric methods comparison between groups was performed with the Mann–Whitney *U* test. Chi-squared test or Fisher's exact test was used for the analysis of categorical variables. A *p*-value of less than .05 was regarded as significant. Statistica 5.1 PL for Windows software (StatSoft Polska, Krakow, Poland) was employed for analyses.

RESULTS

Detailed characteristics of study population are presented in Tables 1 and 2.

Skin Prick Tests

In 64 patients with persistent allergic rhinitis, 59 were sensitized to *D. pteronyssinus*, 58 to *D. farinae*, 21 to cat dander, 22 to dog dander, 22 to grass, 17 to trees, 15 to weeds, 11 to feathers, 13 to *Aspergillus* and *Alternaria*, but sensitization to *Dermatophagoides* spp. predominated over sensitization to other allergens.

In the group of asthmatics 30 subjects were sensitized to *D. pteronyssinus*, 28 to *D. farinae*, 16 to cat dander, 11 to dog dander, 23 to grass, 12 to trees, 20 to weeds, 12 to feathers, 7 to *Aspergillus* and *Alternaria*; however, sensitization to *Dermatophagoides* spp. predominated over sensitization to other allergens.

Total Serum IgE

Total serum IgE was significantly higher in patients with persistent allergic rhinitis (141.49 ± 23.82 IU/ml) than in the group with nonatopic rhinitis (25.58 ± 3.9 IU/ml, $p < .0001$) and healthy control (29.9 ± 4.2 IU/ml, $p < .0001$) (Figure 1).

Serum concentration of the total IgE was highest in patients suffering from severe asthma who were not treated with systemic glucocorticosteroids (group 3, 392.66 ± 85.0 IU/ml), was lower in patients with mild–moderate asthma (group 1, 209.9 ± 37.42 IU/ml), and the lowest in patients with severe asthma receiving systemic steroid therapy (group 5, 133.93 ± 35.18 IU/ml), however, was higher than in corresponding group of nonatopic asthmatics (group 2, 33.26 ± 7.75 IU/ml, $p < .001$ vs. group 1; group 4, 31.32 ± 9.73 IU/ml $p < .05$ vs. group 3; and group 6, 39.26 ± 10.14 IU/ml $p < .05$ vs. group 5) (Figure 1).

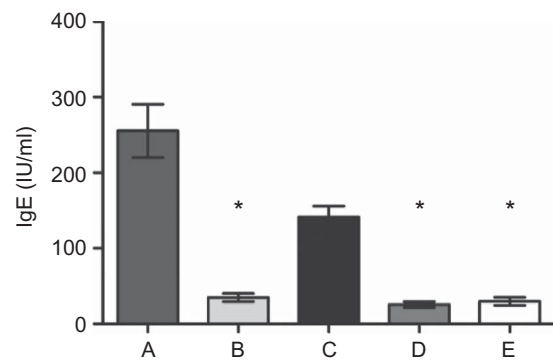


FIGURE 1.—Total serum immunoglobulin E (IgE) (IU/ml) in subjects with persistent atopic asthma (A), nonatopic asthma (B), atopic rhinitis (C), nonatopic rhinitis (D), and healthy control (E).

Notes: Data are presented as mean $\pm$ SEM.

* $p < .0001$ for B versus A, D versus C, and E versus A and B, respectively.

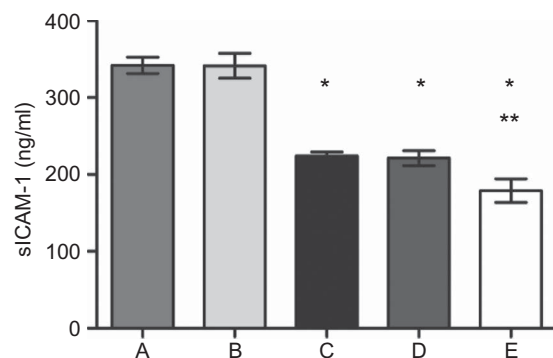


FIGURE 2.—Concentration of soluble ICAM-1 (sICAM-1) (ng/ml) in subjects with persistent atopic asthma (A), nonatopic asthma (B), atopic rhinitis (C), nonatopic rhinitis (D), and healthy control (E).

Notes: Data are presented as mean $\pm$ SEM.

* $p < .0001$ for C, D, and E versus A and B, ** $p < .05$ for E versus C and D, respectively.

sICAM-1 Concentration in Serum

sICAM-1 levels were the lowest in the control group (178.8 ± 12.2 ng/ml) (Figure 2). There were no significant differences in sICAM-1 levels between subjects with persistent allergic rhinitis (224.02 ± 4.95 ng/ml) and subjects with nonatopic rhinitis (221.08 ± 9.85 ng/ml, $p > .05$) (Figure 2).

In asthmatics, the concentration of sICAM-1 was higher than in rhinitic patients. There was no significant difference in sICAM-1 levels between all patients with atopic asthma ($n = 63$, 341.78 ± 10.6 ng/ml) when we compared with all nonatopic asthmatics ($n = 27$, 341.26 ± 16.18 ng/ml, $p > .05$). sICAM-1 levels were the highest in patients with severe atopic and nonatopic asthma who were not treated with systemic glucocorticosteroids and significantly higher in comparison with patients with mild/moderate atopic and nonatopic asthma and patients with severe atopic/nonatopic asthma who were treated with systemic glucocorticosteroids. Furthermore, there were no significant differences in sICAM-1 levels between atopic and nonatopic subjects in each group of asthmatic patients. sICAM-1 concentrations in ng/ml were as follows: group 1, 306.22 ± 10.78 versus

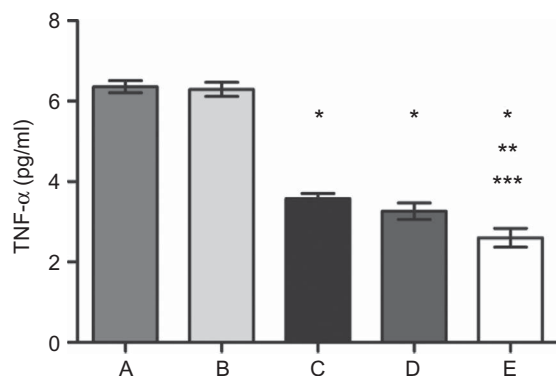


FIGURE 3.—Concentration of TNF- α (pg/ml) in subjects with persistent atopic asthma (A), nonatopic asthma (B), atopic rhinitis (C), nonatopic rhinitis (D), and healthy control (E).

Notes: Data are presented as mean $\pm$ SEM.

* $p < .0001$ for C, D, and E versus A and B, ** $p < .001$ for E versus C, and *** $p < .05$ for E versus D, respectively.

group 2, 326.39 ± 11.46 ($p > .05$); group 3, 418.03 ± 16.74 versus group 4, 468.09 ± 50.59 ($p > .05$); group 5, 320.66 ± 25.31 versus group 6, 308.09 ± 26.79 ($p > .05$) (Figure 2).

TNF- α Concentration in Serum

There was no significant difference in TNF- α levels between all patients with atopic asthma ($n = 63$, 6.36 ± 0.15 pg/ml) compared with all patients with nonatopic asthma ($n = 27$, 6.29 ± 0.18 pg/ml, $p > 0.05$). TNF- α concentration was the highest in patients with severe atopic asthma who were not treated with systemic glucocorticosteroids and the lowest in patients with severe asthma who underwent such therapy; however, the difference was not statistically significant ($p > .05$). Furthermore, there were no significant differences between groups of atopic and the corresponding nonatopic patients: group 1, 6.18 ± 0.14 pg/ml versus group 2, 6.11 ± 0.27 pg/ml ($p > .05$); group 3, 6.89 ± 0.38 pg/ml versus group 4, 6.44 ± 0.18 pg/ml ($p > .05$); group 5, 5.92 ± 0.29 pg/ml versus group 6, 6.49 ± 0.30 pg/ml ($p > .05$) (Figure 3).

In rhinitic patients the concentration of TNF- α was lower than in patients suffering from asthma, and there was no difference between atopic and nonatopic subjects (3.57 ± 0.12 pg/ml and 3.26 ± 0.21 pg/ml for atopic and nonatopic patients, respectively, $p > .05$) (Figure 3).

Both patients with asthma (atopic or nonatopic) and rhinitis (atopic and nonatopic) had higher levels of TNF- α when compared with the healthy group (2.6 ± 0.18 pg/ml) (Figure 3).

DISCUSSION

In this study, we examined the relationship between the presence of atopy and serum levels of sICAM-1 and TNF- α separately in atopic and nonatopic patients with rhinitis or asthma. Although total IgE concentration was highest in atopic individuals, there was no correlation between the serum concentration of sICAM-1 and TNF- α with the atopy, defined here as a positive history, positive results in skin prick tests, and high

total IgE concentration. Both atopic and nonatopic patients with rhinitis or asthma in corresponding groups had the same concentrations of sICAM-1 and TNF- α .

Adhesion molecules (ICAM-1) and TNF- α are involved in the development of airway allergic inflammation in both rhinitis and asthma. ICAM-1 mediates leukocyte adhesion, initiates intercellular signaling events, and modulates cell activation, proliferation, and cytokine production (6). ICAM-1 expression is upregulated in patients with chronic allergic rhinitis and asthma as compared with healthy control (14,15) and further increases in asthma exacerbations (16,17). Concentration of sICAM-1 correlated with BHR and asthma severity (18–20). These results as well as a reduction of sICAM-1 concentrations during the treatment with oral prednisolone in patients with asthma exacerbations (16) support the hypothesis that increased serum sICAM-1 levels reflect more pronounced inflammation in human airways. Therefore, sICAM-1 together with exhaled nitric oxide, blood eosinophils, and serum eosinophil cationic protein (ECP) (21–23) may serve as a useful marker for monitoring allergic inflammation and efficacy of the treatment.

TNF- α is a principal mediator of the acute inflammatory response against many microbes and plays an important role in allergic inflammation. The major source of TNF- α are activated mononuclear phagocytes and natural killer cells, T-cells, and mast cells. In allergic inflammation TNF- α is required for the production of Th2-type cytokines, the induction of adhesion molecules (ICAM-1, ELAM-1, VCAM-1) and the migration of leukocytes to the sites of inflammation (24). In TNF- α knockout mice, the induction of allergic rhinitis was strongly inhibited due to severe impairment of endothelial leukocyte adhesion molecule-1 and vascular cell adhesion molecule-1 expression (7). Concentration of TNF- α is higher in atopic patients with asthma and allergic rhinitis than in healthy control (18), and in the induced sputum TNF- α levels correlated with BHR and asthma severity in young adults (25) and correlated with rhinitis (18) but not asthma severity (18,19).

In our study, concentrations of sICAM-1 and TNF- α were generally higher in asthmatics than in rhinitic patients and were predominant in patients with severe asthma who were not treated with systemic glucocorticosteroids, regardless of the presence of atopy. There were no differences in sICAM-1 and TNF- α concentrations both in patients with rhinitis and in patients with asthma when we compared corresponding groups of patients arranged according to the atopy, severity of disease, and treatment. Furthermore, the use of systemic steroids resulted in the prompt inhibition of allergic inflammation in the airways reflected by reduction of sICAM-1 and TNF- α concentrations similarly in atopic and nonatopic asthma. Both atopic and nonatopic patients suffering from rhinitis had the same total nasal and total eye symptom scores, whereas nonatopic asthmatics demonstrated higher asthma symptom score and lower FEV₁ than their atopic counterparts.

These data support the observation that atopic and nonatopic rhinitis or asthma, regardless of the initial IgE production, are similar in later stages. In both types of asthma, similar cells infiltrate areas of inflammation and produce the same cytokines and chemokines (26–29). Concentrations of IL-4, IL-5, and IL-13 were higher in both atopic and nonatopic asthmatics compared with healthy controls (30,31), and there were no differences in the expression of eotaxin, eotaxin-2, regulated on activation, normal T-cell expressed and secreted (RANTES), monocyte chemoattractant protein-3 (MCP-3), and MCP-4 in bronchial biopsies in atopic asthma compared with nonatopic asthma (32). Interestingly, in nonatopic asthma a significant local IgE production in the airways was observed (33). IgE-mediated mechanism could be responsible for the occurrence of symptoms in asthma previously described as nonatopic one. IgE, although is crucial for initiation of early phase of allergic inflammation in atopic patients and enhances airways inflammation and bronchial responsiveness (34), is not strictly necessary for the induction of late-phase inflammation (34). The allergic inflammation and BHR may develop independently from the atopic background which explains why we were unable to find any differences in the serum levels of sICAM-1 and TNF- α in atopic and nonatopic patients.

From a clinical point of view some studies indicate that atopic and nonatopic asthma are different. Nonatopic asthma is connected with the presence of nasal polyposis and hypersensitivity to aspirin and is more often reported in women and adults, whereas atopic asthma usually affects both sexes and begins at a young age. However, the hypothesis that nonatopic asthma is connected to greater severity of the disease is controversial. We found that severe asthma is more frequent in nonatopic subjects than in atopic and nonatopic patients who more often required systemic steroids and had lower FEV₁ value. A similar observation was reported in Epidemiological study on the Genetics and Environment of Asthma study (35) where the authors demonstrated that FEV₁ was higher in allergic asthmatics compared with nonallergic asthmatics and the use of systemic steroids was more frequent and the severity score was higher in nonallergic asthmatics. The multivariate analysis showed that older age, female sex, sinus polyposis, as well as FEV₁ below 80% of the predicted value increased the risk of displaying nonatopic asthma, whereas a history of hay fever, seasonal exacerbation of asthma, and asthma duration lowered this risk. Ulrik et al. (36) found a greater annual decline in lung function in nonallergic asthmatics than in allergic asthmatics. However, Inouye et al. revealed that the severity of asthma was relatively similar in skin test-positive and skin test-negative patients (37).

CONCLUSION

The results of our study support the theory that although IgE is essential for the early phase initiation of allergic inflammation in atopic individuals, it is not necessary

for the induction and maintenance of the late-phase inflammation. The inflammatory responses observed were similar in both atopic and non-atopic patients.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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