

## THE INFLUENCE OF ATOPY ON sICAM-1 SERUM LEVELS IN PATIENTS WITH ALLERGIC RHINITIS AND BRONCHIAL ASTHMA

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**Summary:** It has been shown that adhesive molecules are involved in inflammatory diseases of the lungs such as bronchial asthma. The purpose of the study was to measure and establish possible difference in serum levels of soluble ICAM-1 in 42 atopic patients (patients with allergic rhinitis and patients with bronchial asthma) in comparison with 28 patients without atopy (patients with asthma without rhinitis); whether there is a difference in sICAM-1 levels between groups of 26 patients with allergic rhinitis and asthma in comparison with group of 16 patients with allergic rhinitis only and also in comparison with 10 healthy controls. Results of the study have substantiated statistically significant difference in sICAM-1 levels between all groups of patients in comparison to healthy control, but no statistically significant difference in sICAM-1 levels between patients with and without atopy ( $Z=-1.738$ ) or between patients with allergic rhinitis and bronchial asthma in comparison with group of patients with allergic rhinitis only ( $Z=0.00$ ). ICAM-1 is an important marker of inflammation in patients with allergic rhinitis as well as in those with bronchial asthma. Atopic status does not influence differences in sICAM-1 levels. Although mean sICAM-1 levels were higher in patients with allergic rhinitis and bronchial asthma (312.71 ng/mL) in comparison with mean sICAM-1 levels in patients with allergic rhinitis only (279.69 ng/mL), no statistically significant difference was noted in sICAM-1 levels between these groups of subjects, i.e. asthma itself did not contribute to statistically significant increase of sICAM-1 levels.

**Key words:** intercellular adhesive molecule 1, allergic rhinitis, bronchial asthma, atopy

### Introduction

Preliminary studies have suggested that intercellular adhesive molecule 1 (ICAM-1; CD54) may be involved in pathogenesis of asthma (1). Soluble form of the intercellular adhesive molecule 1 (sICAM-1) was detected in elevated levels in the sera of adult patients with some inflammatory, immune or malignant diseases (1). It originates from proteolytic cleavage of membrane ICAM-1 (m ICAM-1) (2). In asthmatic patients epithelial cells of airways may express increased amounts of ICAM-1 molecule, which is one of the responses to different stimuli such as local cytokines, infectious agents, air pollutants, allergens. Their res-

ponse to these stimuli alters the immune and inflammatory environment that is critical in diseases such as bronchial asthma.

The aim of the study was to measure and establish the possible difference in sICAM-1 levels in sera of patients with atopy (patients with allergic rhinitis and patients with allergic rhinitis and bronchial asthma) in comparison with the group of patients without atopy (patients with asthma without rhinitis) as well as possible differences in sICAM-1 levels between groups of patients with allergic rhinitis and asthma in comparison with patients with allergic rhinitis only.

### Material and Methods

Our study comprised patients with allergic rhinitis and bronchial asthma. The diagnosis of bronchial asthma was established following the guidelines for diagnosis and treatment of asthma of the international expert group of the National Institute of Health and

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National Institute of Heart, Lungs and Blood, Bethesda, May 1997, suppl. 2002 (3). All patients had positive results of metacholine and/or Ventolin test. Sensitization to standard inhaling allergens was tested by skin prick test in all patients.

All patients were subjected to physical medical examination. Pulmonary function before blood sampling was measured using Autospir Discom-14 Chest Corporation Tokyo, Japan. In addition to history, skin tests and determination of serum IgE, patients with allergic rhinitis were subjected to *in vivo* specific rhino-provocative tests to evidence the presence of allergic rhinitis.

The sICAM-1 levels were measured in blood samples obtained after the cubital vein puncture using vacutainer, without EDTA addition. The sample was left to coagulate at room temperature for 60–120 minutes. After that the samples were centrifuged at 1300 g for 10 minutes at room temperature. The separated serum was stored at  $-20^{\circ}\text{C}$  until the actual analysis. ELISA was used for the sICAM-1 serum level determination. The commercial Parameter human sICAM-1 immunoassay (ELISA, R&D Systems Inc. Minneapolis, USA) was used. The sICAM-1 serum levels were expressed in ng/mL. The lowest detectable value of serum sICAM-1 was 0.35 ng/mL (following the manufacturers instructions).

The subjects were classified into following groups: 16 with allergic rhinitis, 26 with allergic rhinitis and bronchial asthma (all of them combined composed the group with atopy); 28 patients bronchial asthma without allergic rhinitis (composing the group without atopy). The control group was composed of 10 healthy volunteers, mean age 37 years without history of allergy, asthma, allergic rhinitis, atopic dermatitis or any other significant disease.

Statistical analysis was conducted using EPI INFO ver. 10 program package. Statistical differences were calculated using non-parametric Mann-Whitney and Kruskal-Wallis tests. Correlations among different parameters were conducted using the Spearman's rank correlation coefficient (4, 5).

## Results

The control group of healthy subjects had mean sICAM-1 values of 226.64 ng/mL, coinciding with control values stated by the manufacturer (R&D Systems). The mean sICAM-1 levels in patients with and without atopy were 300.10 ng/mL and 315.00 ng/mL, respectively. The correlation coefficient of sICAM-1 levels between groups of healthy subjects and patients with and without atopy was  $H=12.072$ ,  $p<0.01$ , suggesting statistically significant difference of sICAM-1 levels between the groups of subjects.

The correlation coefficient of sICAM-1 levels between groups with atopy (patients with allergic rhinitis

and patients with asthma and allergic rhinitis) and healthy subjects was  $Z_1=-2.670$ ,  $p<0.01$ , suggesting highly statistically significant difference between the groups, i.e. sICAM-1 level was significantly higher in patients with atopy than in healthy controls.

The correlation coefficient of sICAM-1 levels between groups without atopy (patients with bronchial asthma without allergic rhinitis and negative skin prick test) and healthy subjects was  $Z_2=-3.166$ ,  $p<0.01$ , suggesting highly statistically significant difference between the sICAM-1 levels in the groups, i.e. sICAM-1 level was significantly higher in patients with asthma without atopy than in healthy controls. The correlation coefficient of sICAM-1 levels between groups with and without atopy was  $Z_3=-1.738$ ,  $p>0.05$ , suggesting no statistically significant difference between the sICAM-1 levels in the groups, i.e. sICAM-1 serum levels were similar in patients with atopy (allergic rhinitis only and allergic rhinitis with bronchial asthma) and those without atopy (patients with bronchial asthma only), (Table I).

The mean value of sICAM-1 levels in patients with allergic rhinitis was 279.62 ng/mL, while in patients with allergic rhinitis and asthma the level of 312.71 ng/mL was recorded. The mean sICAM-1 level

Table I Mean values of sICAM concentrations in our studies groups

		Group		
		healthy	atopy	atopy free
ICAM-1 (ng/mL)	Valid N	N=10	N=42	N=28
	Mean	226.6	300.10	315.00
	Std Dev.	32.94	136.34	79.26
	Min.	197.0	167.05	190.04
	Max.	301.9	930.65	488.89
H=12.072		$p<0.01$		
$Z_1=-2.670$		$p<0.01$		
$Z_2=-3.166$		$p<0.01$		
$Z_3=-1.738$		$p<0.05$		

Table II Mean values of sICAM concentrations in our studies groups

		Group		
		healthy	rhinitis	asthma and rhinitis
ICAM-1 (ng/mL)	Valid N	N=10	N=16	N=26
	Mean	226.6	279.62	312.71
	Std Dev.	32.94	136.34	168.66
	Min.	197.0	183.14	167.05
	Max.	301.9	376.63	930.65
H=12.072		$p<0.01$		
$Z_1=-2.670$		$p<0.01$		
$Z_2=-3.166$		$p<0.01$		
$Z_3=-1.738$		$p<0.05$		

in healthy subjects was 226.64 ng/mL. The correlation coefficient of sICAM-1 levels between the groups was  $H=7.172$ ,  $p<0.05$ , suggesting the statistically significant difference in sICAM-1 levels between the groups. The correlation coefficient of sICAM-1 levels between the groups of patients with allergic rhinitis and healthy controls was  $Z_4=-2.821$ ,  $p<0.01$ , suggesting the statistically significant difference between the groups, i.e. patients with allergic rhinitis had statistically significantly higher sICAM-1 levels than the healthy controls. The correlation coefficient of sICAM-1 levels between the groups of patients with allergic rhinitis and asthma on one hand and healthy controls on the other was  $Z_5=-2.172$ ,  $p<0.05$ , suggesting the statistically significant difference between the groups, i.e. patients with allergic rhinitis and asthma had higher sICAM-1 levels than the healthy controls. The correlation coefficient of sICAM-1 levels between the groups of patients with allergic rhinitis on one hand and bronchial asthma and allergic rhinitis on the other was  $Z_6=0.00$ ,  $p>0.05$ , suggesting no statistically significant difference between the groups, i.e. sICAM-1 levels were similar in patients with allergic rhinitis only and those suffering from both allergic rhinitis and bronchial asthma (Table II).

## Discussion

Nowadays, there is a general consensus that inflammation is crucial in pathophysiology of respiratory allergic diseases (6). The level of soluble adhesive molecules in the serum reflects the degree of systemic inflammation, but the dynamics of these molecules in the pathogenesis of allergic diseases and their evolution in the course of treatment remain to be evidenced. ICAM-1 may be induced on various cell types using miscellaneous inflammation stimuli (7). Allergic inflammation is associated with ICAM-1 expression on the surface of different cells such as the endothelium, bronchial epithelium and eosinophilic leukocytes (8-11). Induction of expression of these molecules takes place under the influence of various proinflammatory cytokines such as IFN-gamma, IL-1, TNF-alpha and others.

The purpose of the study was to measure and compare levels of soluble ICAM-1 in the sera of atopic patients non-atopic patients and to compare the levels with the sICAM-1 levels in healthy controls. The mean sICAM-1 levels in healthy controls was 226.64 ng/mL. Shiota and associates reported somewhat higher mean sICAM-1 value in healthy volunteers, i.e. 260.90 ng/mL. It is possible that the difference in the number of healthy volunteers (10 vs. 39) contributed to the difference in the value obtained.

The mean value of sICAM-1 levels in our atopic patients (all patients with allergic rhinitis and patients with both allergic rhinitis and bronchial asthma) was 300.10 ng/mL as compared with 315.00 ng/mL meas-

ured non-atopic patients (bronchial asthma without rhinitis). Similar values in asthmatic patients were reported by Shiota and associates (12). Analysis of the levels of sICAM-1 between the groups of atopic patients and healthy controls as well as the difference between non-atopic group and healthy controls has revealed the presence of statistically significant difference. This actually means that atopic and non-atopic patients had statistically significant levels of sICAM-1 in the sera in comparison with healthy controls. This finding is in concert with referential data (1, 13, 14), substantiating the hypothesis on ICAM-1 as a marker of inflammation in respiratory diseases. However, analysis of correlation of sICAM-1 levels between groups of atopic vs. non-atopic patients failed to substantiate the statistically significant difference, i.e., both atopic and non-atopic patients had similar sICAM-1 levels in the respective sera. Laan and associates (15) obtained similar values in pediatric population, and Figen Do'Egu and associates (16) failed to identify any statistically significant differences in sICAM-1 levels between atopic and non-atopic children.

Results of our study have substantiated the presence of statistically significant difference in sICAM-1 values of patients with allergic rhinitis in comparison with healthy controls. In a study on a group of patients with allergic rhinoconjunctivitis Turgay et al. (17) reported no statistically significant difference between their sICAM-1 levels and healthy controls, but men with allergic rhinoconjunctivitis had higher values of sICAM-1 levels than in women, and in comparison with healthy controls. The sICAM-1 levels were higher in patients with allergic rhinoconjunctivitis that had higher symptom score (17). Kato and associates (18) reported that the level of sICAM-1 in the sera of patients with polynosis was up-regulated in the early season in comparison with healthy control. However, Chia-Ming Liu and associates (19) found overlapping values in sICAM-1 levels of patients with allergic perennial rhinitis and healthy controls. He explained the phenomenon by the target organ size (the nose) that is substantially lower in comparison with target surfaces of other organs such as the lungs and skin.

The reason for the differences in sICAM-1 levels in our allergic rhinitis patients in comparison with healthy control may lie in the »minimum persistent inflammation« present in patients hypersensitive to mite, that have it all the year round even in absence of symptoms (20). Also, the minimum exposure to allergens in natural conditions may lead to the occurrence of differences in sICAM-1 levels.

Our study has also substantiated the presence of statistically significant difference in sICAM-1 levels between groups of patients with atopy (allergic rhinitis and allergic rhinitis combined with asthma) and group of healthy volunteers, complying with referential data. However, in spite of the notable difference in mean sICAM-1 levels in patients with asthma versus patients

with allergic rhinitis only (312.71 ng/mL vs. 279.62 ng/mL) there was no statistically significant difference in sICAM-1 levels between these groups of patients. The reason may lie in heterogeneous composition of the groups where patients with bronchial asthma mainly used the therapy of inhaling glyocorticosteroids that may affect the down-regulation of ICAM-1 molecules (13, 16, 21–23).

The results of the study have substantiated that sICAM-1 is a marker of inflammation in both patients with bronchial asthma and those with allergic rhinitis, but that atopy itself does not influence the higher sICAM-1 levels in comparison with non-atopic patients. Also, in our study asthma did not contribute significantly to the total sICAM-1 levels. Naturally, future studies are necessitated for better elucidation of the function and regulatory mechanisms of serum ICAM-1.

## UTICAJ ATOPIJE NA NIVO sICAM-1 U SERUMU KOD PACIJENATA SA ALERGIJSKIM RINITISOM I BRONHIJALNOM ASTMOM

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*Kratak sadržaj:* Poznato je da su adhezivni molekuli uključeni u inflamacione bolesti pluća kao što je bronhijalna astma. Cilj ovog rada je bio da se izmeri i utvrdi da li postoji razlika u koncentracijama solubilnog ICAM-1 u serumu 42 bolesnika sa atopijom (bolesnici sa alergijskim rinitisom i bolesnici sa bronhijalnom astmom) u odnosu na grupu od 28 bolesnika bez atopije (bolesnici sa astmom bez rinitisa) da li postoji razlika u koncentracijama sICAM-1 među grupama od 26 bolesnika sa alergijskim rinitisom i astmom u odnosu na 16 bolesnika samo sa alergijskim rinitisom kao i u odnosu na 10 zdravih kontrola. Rezultati rada su pokazali da postoji statistički značajna razlika u koncentracijama sICAM-1 svih pomenutih grupa ispitanika u odnosu na zdravu kontrolu, ali da ne postoji statistički značajna razlika koncentracija sICAM-1 među grupama bolesnika sa atopijom i bez atopije ( $Z = -1,738$ ) kao ni među grupama ispitanika sa alergijskim rinitisom i bronhijalnom astmom u odnosu na grupu ispitanika samo sa alergijskim rinitisom ( $Z = 0,00$ ). sICAM-1 predstavlja značajan marker inflamacije i kod bolesnika sa alergijskim rinitisom kao i kod onih sa bronhijalnom astmom. Atopijski status ne utiče na razlike u koncentracijama sICAM-1. Iako su srednje vrednosti koncentracija sICAM-1 bile više kod bolesnika sa alergijskim rinitisom i bronhijalnom astmom (312,71 ng/mL) u odnosu na srednje koncentracije sICAM-1 kod bolesnika samo sa alergijskim rinitisom (279,62 ng/mL), nije postojala statistički značajna razlika u koncentracijama sICAM-1 među ovim grupama ispitanika, tj. sama astma nije doprinosila statistički značajnijem povećanju koncentracija sICAM-1.

*Ključne reči:* intercelularni adhezivni molekul 1, alergijski rinitis, bronhijalna astma, atopija

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