RESEARCH ARTICLES

SOLUBLE INTERCELLULAR ADHESION MOLECULE-1 (sICAM-1) AND SOLUBLE E-SELECTIN (sE-SELECTIN) IN SERA FROM PATIENTS WITH EXERCISE-INDUCED ASTHMA

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SUMMARY :

Purpose : *The role of inflammation in the pathogenesis of exercise-induced asthma remains unclear. A study was therefore undertaken to investigate the role of inflammation by measuring serum concentrations of sICAM-1 and sE-selectin in patients with exercise-induced asthma.* ***Methods :*** *Pre-exercise, 1 hour and 18 hours post-exercise serum samples were obtained from 10 healthy controls, 10 patients with exercise-induced asthma (EIA[+]), and 10 patients with asthma without exercise-induced asthma (EIA[-]). To determine whether exercise-induced asthma is associated with increased levels of soluble intercellular adhesion molecule-1 (sICAM-1) and sE-selectin, the concentrations of these adhesion molecules were measured in sera of controls and asthmatic patients.* ***Results :*** *The mean pre-exercise serum concentrations of sICAM-1 and sE-selectin in control group were not significantly different from the EIA(+) and EIA(-) patients. The mean (SD) sICAM-1 concentrations in pre-exercise, 1 hour, and 18 hours after exercise periods were 465.50 (263.23) ng/mL, 493.28 (150.96) ng/mL and 521.07 (199.49) ng/mL respectively for EIA(+) patients and 573.21 (309.63) ng/mL, 625.02 (254.45) ng/mL and 547.93 (195.53) ng/mL respectively for EIA(-) patients. The mean levels of sE-selectin were 48.30 (24.76) ng/mL, 47.61 (21.42) ng/mL and 46.12 (21.25) ng/mL respectively for EIA(+) patients and 53.13 (25.50) ng/mL, 49.77 (27.92) ng/mL and 50.88 (26.13) ng/mL respectively for EIA(-) patients. There were no significant difference in serum sICAM-1 and sE-selectin levels between EIA(+) and EIA(-) patients and between pre- and post-exercise levels in each group.* ***Conclusions :*** *These findings suggest that exercise-induced asthma is not associated with the increased serum concentrations of sICAM-1 and sE-selectin.*

Key Words: *Cell Adhesion Molecules, Intercellular Adhesion Molecule-1, E-Selectin, Exercise-Induced Asthma.*

INTRODUCTION

The mechanism of increased airflow obstruction after exercise in patients with asthma remains unclear. Exercise-induced asthma has been related to hyperventilation (1) and subsequent airway cooling (2) and to the rapid rewarming of airways during the recovery period (3). The role of inflammatory cells and mediators in the pathogenesis of exercise-induced asthma also remains controversial. There were conflicting results about the role of inflammation in EIA (4-11).

The recruitment of inflammatory cells to inflamed tissues depends on the function of

adhesive molecules of the leukocytes and vascular endothelium (12). The intercellular adhesion molecule-1 (ICAM-1), a 80-110 kDa glycoprotein and a member of the immunoglobulin supergene family with five-domain structures, has been found to be a ligand for the lymphocyte function-associated antigen-1 (LFA-1) and the Mac-1 molecule of the integrin family (13). Upregulation of ICAM-1 expression was observed on the endothelium, the bronchial epithelium and eosinophils (12, 14), suggesting an important role for ICAM-1 in the pathogenesis of bronchial asthma. E-selectin is a cell surface glycoprotein with a molecular weight of 110-115 kDa which binds Sialyl-Lex, on leukocyte surface (15). It plays an important role in the influx of leukocytes in allergic inflammation of airways (16).

Recently, soluble forms of these adhesion molecules have been identified in the serum of healthy subjects and various diseases. Their levels may be increased during inflammatory disease or malignancy (17-20). sICAM-1 contains most of the structure of the extracellular portion of membrane-bound ICAM-1, thus, sICAM-1 could potentially have physiologic functions.

In the present study, the concentrations of sICAM-1 and sE-selectin in sera of asthmatic patients were measured to determine whether these adhesion molecules exist in the sera of asthmatic patients and whether the concentrations of these molecules are elevated in EIA(+) patients when compared with EIA(-) patients and control subjects.

MATERIALS AND METHODS

Patients and healthy volunteers

The study group consisted of three groups. First group comprised 10 healthy adult volunteers (eight women and two men; average age, 34 years; range 23 and 57 years). The second group comprised 10 adult subjects with clinical history of EIA and positive exercise challenge test defined as a >10 % fall in FEV1 after maximal exercise (seven women and three men; average age, 39 years; range 18 and 63 years). The third group comprised 10 adults with asthma without EIA (six women and four men; average age, 37 years; range 21 and 50 years). Patients with an upper respiratory infection within six weeks before testing, an episode of asthma requiring hospitalization within the previous six weeks, pregnancy or cardiorespiratory disease other than asthma were excluded. Their mean pre-exercise percentage of predicted FEV1 were 109 (range 90 and 128), 97 (range 69 and 108), and 99 (range 74 and 114), respectively which were not significantly different in three groups (Table 1). Four patients from EIA(-) group and 3 patients from EIA(+) group were atopic. They had positive skin prick tests to one of five common allergens (Dermatophagoides pteronyssinus, house dust, mixed pollen grasses and cat dander). All asthmatic patients had mild persistent asthma, and the average duration of the symptoms was 5.3 years. They were all recieving inhaled beta-2 agonists as needed. Six patients with EIA and 5 patients without EIA were taking inhaler steroids and none of them used teophylline. All subjects were non-smokers. All asthmatic patients met the criteria of the American

	Control (n=10)	EIA(-) (n=10)	EIA(+) (n=10)
Age/yr (mean (SD)	34.30 (9.37)	37.00 (8.26)	39.20 (14.59)
Sex (M/F)	2/8	4/6	3/7
Atopics	-	4	3
Patients taking inhaler steroids	-	5	6
FEV_1 (%predicted)			
(mean (SD))	109.70 (12.26)	99.90 (17.84)	97.30 (19.32)
PEF (% predicted)			
(mean (SD))	105.40 (22.47)	99.10 (18.12)	83.70 (17.03)

* There were no significant difference between the groups

Table 1 : Characteristics of asthmatic patients and control subjects*

Thoracic Society for the diagnosis of asthma and none of the healthy volunteers had a history of asthma (21). Written informed consent was obtained from each individual before participation.

Endothelial adhesion molecules show a time course of expression when activated with inflammatory mediators. The expression of E-selectin and ICAM-1 are maximum at 3rd and 18th hours of post-cytokine stimulation, respectively (22). Depending on these findings serial serum samples were obtained from controls and asthmatic patients before, 1 hour and 18 hours after exercise testing to asses changes in sICAM-1 and sE-selectin levels with exercise.

Exercise challenge

The exercise challenges consisted of incremental exercise on a bicycle ergometer (Ergo-Metrics 900 Sensormedics) at a work load sufficient to maintain the heart rate between 160 and 180 beats per minute (80% of the maximum predicted) for 6 minutes. Heart rate and blood pressure were monitorized during and after exercise. The air-conditioned room temperature ranged from 22° C to 25° C, and the relative humidity ranged from 45 percent to 55 percent. The subjects refrained from taking any bronchodilating medication for 8 hours and caffeine for 24 hours before coming to the laboratory. The response was measured by the FEV1 before (baseline value) and 5, 10, 15, 20, 25 and 30 minutes after exercise test (Sensormedics model 2200). The airway response to exercise was calculated as the maximum decline in FEV1 , from the prechallenge value, expressed as a percentage.

Positive result defined as >10 % fall in FEV1 after maximal exercise (23).

PEF was measured by Wright's peak flow meter (best of three attempts) immediately before and one hour after exercise. Thereafter it was measured once hourly for the rest of the day to detect a possible LAR.

Measurement of sICAM-1 and sE-selectin

Soluble ICAM-1 and E-selectin were measured with a sandwich enzyme-linked immunosorbent assay (ELISA) by using ICAM-1 test kit (T Cell Diagnostics Inc, Woburn) and E-selectin test kit (R&D systems, Minneapolis) respectively. All sera were stored -40° C until sICAM-1 and sE-selectin were measured.

Statistical methods

All data were expressed as the mean (SD). Differences in baseline sICAM-1 and sE-selectin levels between the three groups were compared by applying Kruskal-Wallis analyses of variance. The differences in baseline soluble adhesion molecule levels between the patients who were treated with inhaled steroids and who were not treated were compared by using Mann-Whitney U test. To determine the effect of regular inhaled corticosteroid treatment on post-exercise sICAM-1 and sE-selectin levels, the first levels compared with those the second and the third levels in all groups. A two way repeated measures ANOVA was used to detect differences. To determine the effect of exercise on soluble adhesion molecules, sICAM-1 and sE-selectin levels were measured before exercise, 1 hour and 18 hours after exercise and first measurements were compared with those of second and third measurements. A one-way repeated measures ANOVA was used to detect differences.

The differences were considered to be statistically significant when the p value less than or equal to 0.05. All statistical calculations were performed on a personal computer by means of the statistical package, SPSS V6.

RESULTS

Basal levels of sICAM-1 and sE-selectin

Soluble ICAM-1 and E-selectin were detected in serum from all normal volunteers and asthmatic patients. The pre-exercise serum concentrations of sICAM-1 in the control subjects, EIA(-) asthmatics and EIA(+) asthmatics were 440.02 (246.12) ng/mL, 573.21 (309.63) ng/mL and 465.50 (263.23) ng/mL respectively (Fig 1, Table 2). The mean basal concentrations of sE-selectin in the control group, EIA(-) asthmatics and EIA(+) patients were 46.96 (15.11) ng/ml, 53.13 (25.50) ng/ml, and 48.03 (24.76) ng/ml respectively (Fig 2, Table 2). There were no significant difference in serum sICAM-1 and sE-selectin concentrations between three groups.

Among the asthmatic patients, basal serum sICAM-1 levels of patients those receiving inhaler steroids, 520.80 (316.74) ng/ml (n=11) were not significantly different from those not receiving inhaler steroids, 517.59 (260.09) ng/ml (n=9). Basal serum sE-selectin levels of patients those

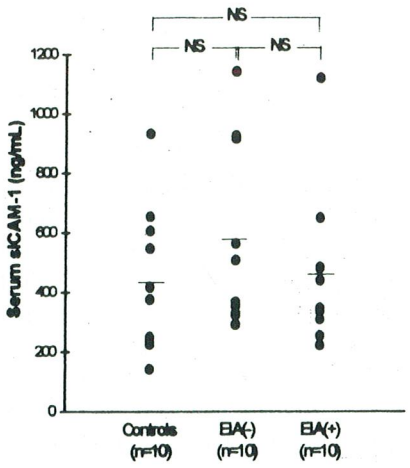

Fig - 1 : Basal levels of s ICAM-1 in sera of healthy controls and asthmatic patients. Horizontal short lines indicate the mean of each group.

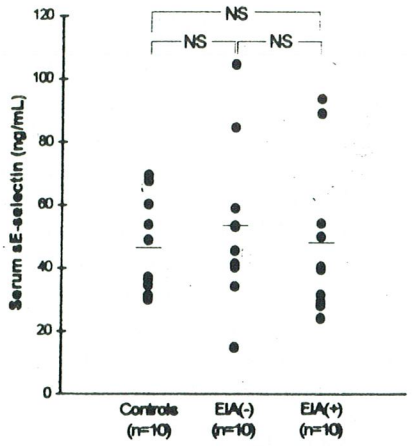

Fig - 2 : Basal levels of sE-selectin in sera of healthy controls and asthmatic patients. Horizontal short lines indicate the mean of each group.

receiving inhaler steroids were not also significantly different from those not receiving steroids (53.23 (29.24) ng/ml vs 47.34 (18.64) ng/ml).

Effect of exercise on serum concentrations of sICAM-1 and sE-selectin

The mean decline of the FEV1 in EIA(+) patients was 16.90 percent. None of the patients developed late asthmatic reaction after exercise. The mean sICAM-1 concentrations in the serum obtained from control group on preexercise, 1 hour and 18 hours after exercise testing were 440.02 (246.12) ng/ml, 447.68 (248.84) ng/ml and 476.19 (278.69) ng/ml respectively which were not significantly different from each other. In EIA(-) patients the mean serum concentrations of sICAM-1 on preexercise, 1 hour and 18 hours after exercise testing were 573.21 (309.63) ng/ml, 625.02 (254.45) ng/ml and 547.93 (195.53) ng/ml respectively which were not differ significantly from each other. In the patients with exercise-induced asthma the mean sICAM-1 concentrations before exercise, 1 hour and 18 hours after exercise testing were 465.50 (263.23) ng/ml, 493.28 (150.96) ng/ml and 521.07 (199.49) ng/ml respectively which were not also significantly different from each other (Fig 3, Table 2).

In the case of sE-selectin, results very similar to those of sICAM-1 were observed. The mean serum sE-selectin concentrations on pre-exercise, 1 hour and 18 hours after exercise were 46.96 (15.11) ng/ml, 44.98 (17.64) ng/ml and 46.22 (16.30) ng/ml respectively for control group, 53.13 (25.50) ng/ml, 49.77 (27.92) ng/ml and 50.88 (26.13) ng/ml respectively for EIA(-)patients and 48.30 (24.76)

	Control	EIA(-)	EIA(+)
sICAM-1	**(n:10)**	**(n:10)**	**(n:10)**
Pre-exercise	440.02 (246.12)	573.21 (309.63)	465.50 (263.23)
1 hour after exercise	447.68 (248.84)	625.02 (254.45)	493.28 (150.96)
18 hours after exercise	476.19 (278.69)	547.93 (195.53)	521.07 (199.49)
sE-selectin			
Pre-exercise	46.96 (15.11)	53.13 (25.50)	48.03 (24.76)
1 hour after exercise	44.98 (17.64)	49.77 (27.92)	47.61 (21.42)
18 hours after exercise	46.22 (16.30)	50.88 (26.13)	46.12 (21.25)

Table 2 : Serum sICAM-1 and sE-selectin levels (ng/ml), mean (SD)

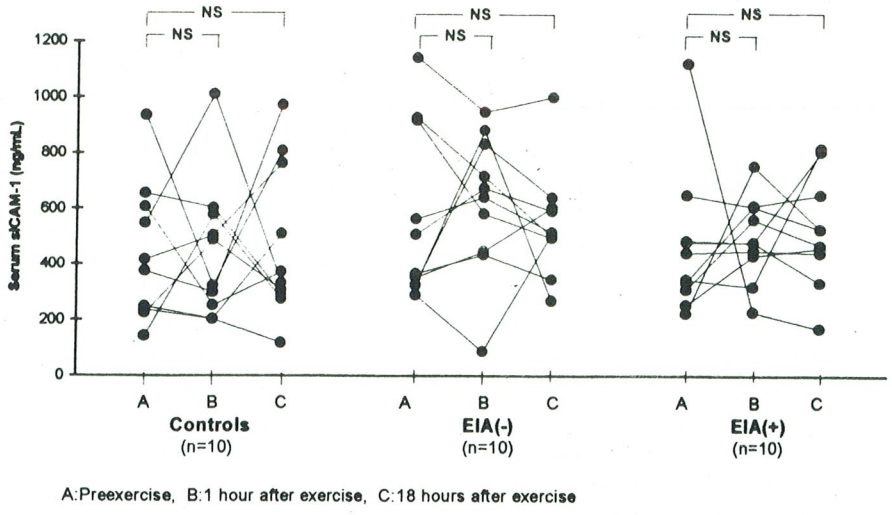

Fig - 3 : Changes of serum sICAM-1 levels in controls, EIA(-) and EIA(+) patients with exercise.

ng/ml, 47.61 (21.42) ng/ml and 46.12 (21.25) ng/ml respectively for EIA(+) patients (Fig 4, table 2). There were no significant difference in serum sE-selectin concentrations between three groups and between pre- and post-exercise levels in each group.

and 46.39 (19.50) ng/ml and 43.49 (20.80) ng/ml for patients those not taking inhaler steroids respectively. There were no significant difference in serum sICAM-1 and sE-selectin concentrations between the two groups and between pre- and post-exercise levels in each group.

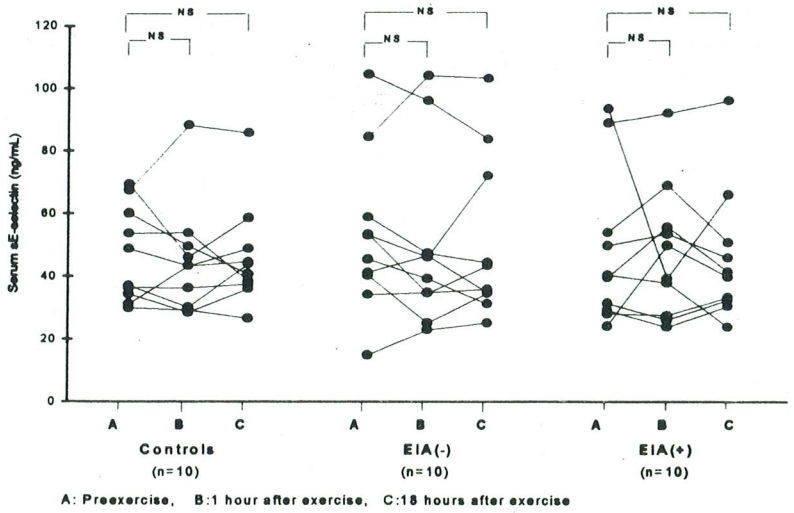

Fig - 4 : Changes of serum sE-selectin levels in controls, EIA(-) and EIA(+) patients with exercise.

The mean one hour and 18 hours post-exercise sICAM-1 levels from asthmatic patients those receiving inhaler steroids were 601.86 (234.65) ng/ml and 553.20 (316.74) ng/ml, from patients those not receiving inhaler steroids were 506.95 (186.88) ng/ml and 511.65 (55.97) ng/ml, respectively. The mean sE-selectin levels at same times were 50.57 (28.35) ng/ml and 52.60 (25.40) ng/ml for patients those receiving inhaled steroids

DISCUSSION

Exercise-induced asthma (EIA) refers to the transient increase in airways resistance that is triggered by vigorous exercise. More precisely, it has been defined as at least a 10% reduction in post-exercise values of peak expiratory flow rate (PEFR) or forced expiratory volume in one second (FEV1) compared with pre-exercise (23). EIA has been

reported to affect 50% to 80% of patients with asthma (24). It is now generally believed, however, that EIA affects all patients with asthma given sufficient exercise intensity (25).

Although there is no consensus about the mechanism of EIA, the most plausible explanations include heat loss, water loss (hyperosmolarity), and airway rewarming.

During tidal breathing to warm and humidify inspired air to alveolar conditions, heat and water are transferred from the mucosa of the upper airways to the incoming air. During exercise, there is a dramatic increase in minute ventilation, the upper airway is bypassed, and inspired air is no longer conditioned by the upper airway. Consequently, the lower respiratory mucosa compensates to complete the conditioning process. This results in both evaporative and conductive cooling of the bronchial mucosa. The increased losses of heat or water or both from the respiratory tract that result from hyperventilation have been suggested as possible triggers of exercise-induced asthma (1). Breathing cold air during exercise has been shown to potentiate exercise-induced asthma (2). Anderson and collegues have suggested that airway water loss is a potent stimulus in exercise-induced asthma, having shown that inhalation of hyperosmolar aerosol can induce bronchoconstriction in patients with asthma (26).

Another explanation for the specific stimulus underlying EIA is postexertional airway rewarming. McFadden et al. postulated that the loss of heat associated with exercise causes a decrease in bronchial blood flow. After the cessation of exercise, reactive hyperemia occurs. This results in edema and congestion, which cause airflow obstruction (3).

The role of inflammatory cells or mediators in the pathogenesis of EIA remains controversial. Earlier studies focused on changes in peripheral blood concentrations of inflammatory mediators with exercise, such as histamine and neutrophil chemotactic factor (NCF). Some studies identified a rise in plasma histamine or NCF with exercise (4), whereas others reported no change (5). Similar disparities were found with urinary leukotrienes. Some studies have demonstrated a rise in urinary leukotrienes (6), whereas others have reported no change (7). Broide et al. found no significant changes in postexercise BAL histamine, tyrptase, LTC4 and PGD2 levels in seven atopic subjects with EIA (8). Jarjour and Calhour performed BALs 1 and 25 hours after exercise and they were unable to demonstrate any significant changes in BAL cellularity, histamine and tryptase levels (9). In contrast Crimi et al found greater BAL eosinophilia and mucosal mast cell degranulation following exercise than methacoline challenge in patients with exercise-induced asthma (10). Venge et al demonstrated similar results. They found small but transient rise in serum ECP levels in patients with EIA but no change in patients without EIA (11). All these studies have shown controversial results about the role of inflammation in EIA.

Adhesion molecules are important in leukocyte migration and effector function at inflammatory foci and therefore may have direct relevance to the pathology of asthma. Vignola et al have found incresed expression of ICAM-1 on bronchial epithelium in asthmatic patients as compared with chronic bronchitics and healthy subjects. They had also found a highly significant correlation between the severity of asthma and percentage of cells spontaneously expressing ICAM-1 molecule (27). All of these studies suggest a role for adhesion molecules in airway inflammation. More recently it was learned that soluble isoforms of these adhesion structures can be found in the circulation (17). Hashimoto et al and Shiota et al. have shown raised levels of soluble ICAM-1 in sera from patients with stable bronchial asthma (18.19). Montefort et al. found that circulating ICAM-1 and E-selectin levels were significantly raised in acute asthma when compared with those observed in stable asthma (28).

Evaluation of soluble form of adhesion molecules might be useful in the investigation and monitoring of airway inflammation in asthma. We have therefore examined sICAM-1 and sE-selectin in the sera of exercise-induced asthmatic patients in order to elucidate possible role of airway inflammation in EIA.

In this study, we have confirmed the presence of detectable concentrations of soluble forms of ICAM-1 and E-selectin in both normal volunteers and asthmatic patients. We have not been able to show any differences in the serum concentrations of these adhesion molecules between normal controls and asthmatic subjects. As these individuals did not suffer from a more severe form

of asthma and were not known to have any respiratory infections, the high concentrations of sICAM-1 or sE-selectin could indicate some other undefined pathophysiological processes. Similarly Montefort et al (28) and Ceyhan et al. (29) had found no significant difference of circulating ICAM-1 between stable asthmatics and control subjects. Although Shiota and colleagues (19) had shown that corticosteroid therapy decreased levels of sICAM-1, we have not been able to demonstrate any difference between the sICAM-1 and sE-selectin levels of patients those recieving inhaled corticosteroids and those not. This effect of corticosteriod also was not observed in the recent study of Montefort et al. (28). Also we could not demonstrate any effect of inhaler corticosteroid therapy on serum soluble adhesion molecules after the exercise.

Asthmatic subjects had no increase in serum sICAM-1 and sE-selectin concentrations in response to exercise. There were no significant differences in serum sICAM-1 and sE-selectin concentrations between those with and without exercise-induced asthma at any time. Exercise was not associated with the increased levels of serum sICAM-1 and sE-selectin. These findings suggest that serum adhesion molecules are not relevant to the mechanism underlying exercise-induced asthma and that some other mechanisms are responsible.

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