

Serum Levels of Soluble CD23 in Patients with Asthma or Rhinitis Monosensitive to *Parietaria*. Its Relation to Total Serum IgE Levels and Eosinophil Cationic Protein during and out of the Pollen Season

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ABSTRACT

The diagnostic value for allergies of the low affinity IgE receptor and its soluble circulating fragment (sCD23) remains unclear. In particular, little is known about seasonal influences on serum sCD23 levels in subjects with pollen allergy. In the present study, to gain insight into pathophysiological role of sCD23, we have analyzed, in blood from patients allergic to Parietaria sCD23, IgE, and eosinophil cationic protein (ECP) serum levels. IgE were assessed as atopy markers and ECP as an inflammation marker.

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Patients were studied during and out of pollen season, and results were compared to those obtained in nonallergic subjects. The study population included 42 nonsmoking outpatients, living in Palermo (Sicily, Italy) or in other west Sicilian towns, with a clinical diagnosis of seasonal asthma or rhinitis and monopositive skin test to Parietaria pollen. The group of asthmatic subjects consisted of 25 patients who had one or more of the usual asthma symptoms (wheezing, dyspnea, and cough) only during the pollen season. The group of rhinitis patients consisted of 17 patients, who, during pollen season, had the nasal symptoms (nasal blockage, sneezing, nasal itching, and rhinorrhoea) but no signs of asthma. As a control group, we studied 10 nonatopic subjects from laboratory staff. They had no history of seasonal or perennial rhinitis, asthma, or urticaria and had negative skin tests to a panel of allergens. Soluble CD23, IgE, and ECP were assessed in blood during and out of pollen season. Total serum IgE levels were clearly higher in atopic patients, as classically established. Concerning sCD23 serum levels, a similar pattern of results was obtained. Accordingly, significant correlations were shown be-

tween the levels of sCD23 and IgE in all groups of patients. A completely different pattern was observed by analyzing serum ECP levels because ECP levels were significantly increased only in asthmatic patients during pollen season. Accordingly, no significant correlations were observed between the levels of sCD23 and those of ECP. Identifying immune factors associated with the development of atopy can enhance our understanding of the *in vivo* mechanisms involved and may have utility in paradigms designed to prevent diseases. As demonstrated by the close correlation with total serum IgE values and the lack of correlation with serum ECP values, serum levels of sCD23 appear to be an additional marker for the diagnosis of atopy but not for the follow-up of allergic diseases. (Allergy and Asthma Proc 20:119–125, 1999)

Asthma and allergic rhinitis are viewed as inflammatory airway diseases involving lymphocyte activation and release of proinflammatory cytokines.^{1,2} T cells control IgE production by B cells and activate nonspecific effector cells that are recruited by chemotactic substances released by mastocytes activated by an IgE-allergen complex.^{3,4} Allergens determine an increased synthesis of IgE and upregulation of CD23, a low-affinity receptor for IgE (FcεRII). It belongs to the C-type lectin family, some members of which have been identified as adhesion molecules, and it is expressed on a wide variety of haematopoietic cell types, including B and T cells, platelets, dendritic cells, monocytes, eosinophils, and Natural Killer cells.^{5–9} The role of the FcεRII might be related to the cell type on which it is expressed. Accordingly, the FcεRII on monocytes, platelets, and eosinophils mediates IgE-dependent cytotoxicity and/or promotes phagocytosis of IgE-coated antigens.^{5–11} It enhances antigen processing by nonspecific uptake of antigen IgE complexes by B cells, that culminates in the highly efficient presentation of antigen fragments to T cells.^{8–10} By interacting with CD21, CD23 appears to mediate a variety of biological activities including cell–cell adhesion, B cell survival in germinal centers, histamine release from basophil, and regulation of IgE synthesis. CD23 is also involved in B cell growth, prothymocyte maturation, myeloid precursor proliferation and inhibition of macrophage migration. Not all of these activities can be attributed to the interaction of CD23 with IgE or CD21.^{6–10,12} The membrane molecule can be transformed into a soluble form (sCD23) by limited proteolysis (i.e., shedding), as well as the cytokine receptors and can then be detected in biological fluids, including serum.^{5–9,12,13} Increased sCD23 serum levels have been found in patients suffering from rhinitis, asthma, and iper-IgE syndrome.^{5,14–17} Increased levels of sCD23 also have been reported in various chronic inflammatory diseases including systemic lupus erythematosus, inflammatory bowel disease, Sjogren's syndrome, glomerulonephritis, and rheumatoid arthritis.¹² Thus, CD23 expression is increased in diseases in which IgE is not involved, and not all the activities of CD23 can be attributed to its interaction with IgE or CD21. That has led to research on novel ligands for CD23, which exhibits a new role as a C-type lectin

binding to Mac-1 and p150,95.¹² This interaction activates macrophages to produce various mediators including proinflammatory cytokines, indicating that CD23, in addition to playing a role in human IgE synthesis, is also involved in inflammatory mechanisms.¹² The diagnostic value for allergies of the low affinity IgE receptor and its soluble circulating fragment remains unclear.^{5,17,18} In particular, little is known about seasonal influences on serum sCD23 levels in subjects with pollen allergy.

In the present study, to gain insight into the pathophysiological role of sCD23, we have analyzed, in blood from patients allergic to *Parietaria* sCD23, IgE, and ECP serum levels. IgE was assessed as an atopy marker and eosinophil cationic protein (ECP) as an inflammation marker.^{19,20} Patients were studied during and out of pollen season and results were compared to those obtained in nonallergic subjects.

Parietaria pollen is more important than Gramineae and *Olea* pollens as a risk for developing bronchial asthma. *Parietaria*, an Urticacea, is the most important rhinitis-provoking plant in Southern Europe. *Parietaria* grows especially on walls inside the towns and has two very long cycles of flowering. The clinical manifestations of pollinosis caused by *Parietaria* are present for long periods, often multiseasonal, particularly in Spring and sometimes also in Autumn.^{21–26}

METHODS

The study population included 42 nonsmoking outpatients, living in Palermo (Sicily, Italy) or in other west Sicilian towns, with clinical diagnosis of seasonal asthma or rhinitis and monopositive to *Parietaria* pollen. The group of asthmatic subjects consisted of 25 patients (16 females, and 9 males, aged 18–47 years, mean age 31.0 ± 8.2) who had one or more of the usual asthma symptoms (wheezing, dyspnea, and cough) only during the pollen season. At the time of the study, both during and out of pollen season, none of the patients were receiving steroid therapy, but were using only inhaled bronchodilators, such as salbutamol, in case of need. However, no patient received any medication for at least 5 days before the study. The group of rhinitis patients consisted of 17 patients (8 females, 9 males, aged 22–44 years, mean age 29.7 ± 4.9) who, during pollen season, had nasal symptoms (nasal blockage, sneezing, nasal itching, and rhinorrhoea) but no signs of asthma. At the time of the study, both during and out of pollen season, none of the patients were receiving nasal steroid or antihistamines therapy, but were using topical decongestant drugs, such as naphazoline, in case of need. However, no patient received any medication for at least 5 days before the study. As a control group, we studied 10 nonatopic subjects from laboratory staff (3 men and 7 women, aged 18–40 years, mean age 31.2 ± 6.5). They had no history of seasonal or perennial rhinitis, asthma, or urticaria and had negative skin prick test to a panel of allergens.

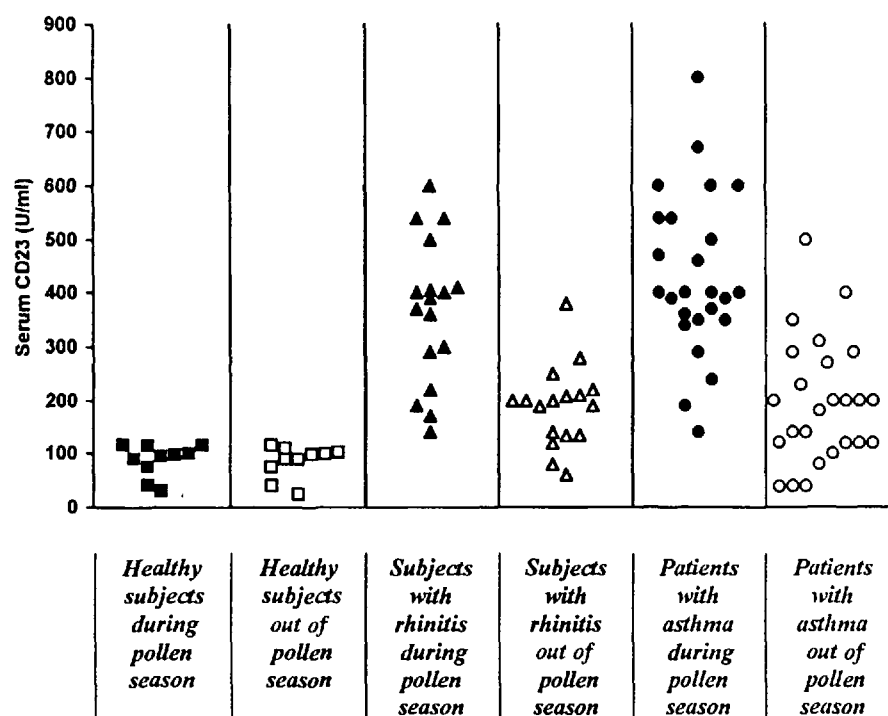


Figure 1. Individual values of serum sCD23 in healthy subjects during (■) and out of (□) pollen season, in patients with rhinitis during (▲) and out of (△) pollen season and in patients with asthma during (●) and out of (○) pollen season. During pollen season, mean $\pm$ SD of serum sCD23 in healthy subjects was 87 ± 30 U/mL, in patients with rhinitis was 366 ± 134 U/mL, and in asthmatic patients was 432 ± 151 U/mL. Out of the pollen season, mean $\pm$ SD of serum sCD23 in healthy subjects was 85 ± 30 U/mL, in patients with rhinitis was 188 ± 75 U/mL, and in asthmatic patients was 297 ± 156 U/mL.

Skin prick tests were performed and evaluated in accordance with European Academy of Allergy and Clinical Immunology Subcommittee on Allergen Standardization and skin tests using a standard allergen panel (Bayer, Milan, Italy). The panel included the following extracts: five pollens (Grass, *Parietaria*, Mugwort, Birch and Olea [1:100 W/V]), two molds (*Alternaria* and *Cladosporium* [10,000 PNU/mL]), two animal danders (cat and dog [1:20 W/V]), two house dust mites (*Dermatophagoides pteronyssinus* and *farinae* [1:20 W/V]), a negative control (glycerinated saline), and a positive control (histamine, 10 mg/mL). A skin test response was regarded as positive if wheal diameters were 3 mm greater than that of the glycerinated saline control.²⁷

Parietaria pollen count per m³ of air were continuously taken with a volumetric pollen trap (Burkard Manufacturing, Rickmansworth, UK) placed on the roof of the Hospital building at a height of approximately 20 m. Microscopic analysis was performed at magnification of 400 $\times$, and results calculated as mean counts per day. The patients were studied during the peak of pollen season, after 2 weeks of peak values that were reached at the end of May. The tests were repeated on the same patients and controls 2 months after the end of pollen season, i.e. in January.²⁸

In May and in January, blood samples were drawn in Vacutainer SST-tubes and, after allowing clotting for 60 minutes at room temperature, the blood was centrifuged for 10 minutes at 1300 g at room temperature. The sera were

frozen at -70°C and analyzed at the end of the study period. Informed consent was obtained from each subject. Serum CD23 levels were measured by a sandwich enzyme-linked immunoassay (Cellfree CD23 Test-Kit-Cell Sciences, Cambridge, MA). The assay was performed according to the manufacturer's instruction, as previously described⁵ and expressed as U/mL (1000 units is defined as the amount of released CD23 present in 1.0 mL of a concentrated T Cell kit reference of supernatants from an Epstein-Barr virus-transformed human B-cell line). Polystyrene microtiter wells were precoated with an anti-CD23 monoclonal antibody. Soluble CD23 in standards or patient's serum binds to coated antibodies, whereas the conjugated antibody binds to a second, distinct epitope on the CD23 molecule completing the sandwich. Absorbance was measured at 492 nm with an ELISA photometer. The detection limit of sCD23 ELISA is 15 U/mL.

Total serum IgE levels were quantified by Phadebas IgE PRIST (Pharmacia, Uppsala, Sweden) and expressed as IU/mL.^{5,28} The detection limit of total serum IgE is 2 U/mL. The assay of serum ECP was performed with a fluorescent enzyme immunoassay using the Pharmacia CAP system (Pharmacia AB, Uppsala, Sweden) and expressed as ng/mL.²⁹ The detection limit of serum ECP is 2 ng/mL. For each assay, standard and samples were performed in duplicate.

Data were expressed as mean values $\pm$ standard deviation. Serum sCD23, total serum IgE, and serum ECP levels

at different time points were examined by variance analysis (ANOVA) for repeated measures using Tukey's honestly significant difference range test, between the groups. A paired *t*-test was used to compare the same patients of each group during and out of pollen season. A difference was considered significant when the *p* value was less than 0.05. Simple regression analysis was used to assess the correlation between serum sCD23 levels and total serum IgE and serum ECP levels during and out pollen season.

RESULTS

No significant age-dependent influence on the serum sCD23 concentrations was observed in the patient population and in the control set (data not shown). Figure 1 shows the serum levels of sCD23 during and out of pollen season in patients with asthma, rhinitis, and in healthy controls. Serum levels of sCD23 in asthmatic patients during the pollen season (432 ± 151 U/mL) were significantly higher than those observed out of pollen season (297 ± 156 U/mL) ($p < 0.001$). In patients with rhinitis during pollen season, the serum levels of sCD23 were significantly higher than those observed out of pollen season (366 ± 134 versus 188 ± 75 U/mL, respectively) ($p < 0.001$). No significant differences were observed between patients with asthma and rhinitis during pollen season, whereas, out of pollen season, the levels of sCD23 were significantly higher in asthmatic patients ($p < 0.05$). In control subjects, no sig-

nificant differences were observed during (87 ± 30 U/mL) and out of pollen season (85 ± 30 U/mL). Comparing asthmatic patients with control subjects, significant differences were observed both during (432 ± 151 U/mL versus 87 ± 30 U/mL) ($p < 0.05$) and out of pollen season (297 ± 156 U/mL versus 85 ± 30 U/mL) ($p < 0.05$), whereas significant differences between patients with rhinitis and control subjects were observed only during the pollen season (366 ± 134 U/mL versus 87 ± 30 U/mL) ($p < 0.05$).

A similar trend was obtained by analyzing total serum IgE values. Figure 2 shows the serum levels of total serum IgE during and out of pollen season in patients with asthma, rhinitis, and in healthy controls. Total serum levels of total IgE in asthmatic patients during pollen season (498 ± 199 IU/mL) were significantly higher than those observed out of pollen season (340 ± 153 IU/mL) ($p < 0.001$). In patients with rhinitis, total serum IgE levels were higher during (388 ± 126 IU/mL) than out of pollen season (246 ± 86 IU/mL) ($p < 0.001$). No significant differences were observed between patients with asthma and rhinitis during the pollen season, whereas, out of pollen season, the levels of total serum IgE were significantly higher in asthmatic patients. In control subjects, no significant differences were observed during (87 ± 19 IU/mL) and out of pollen season (83 ± 29 IU/mL). Serum levels of IgE in asthmatic patients out of pollen season were significantly higher than those observed in control subjects both during (498 ± 199 IU/mL

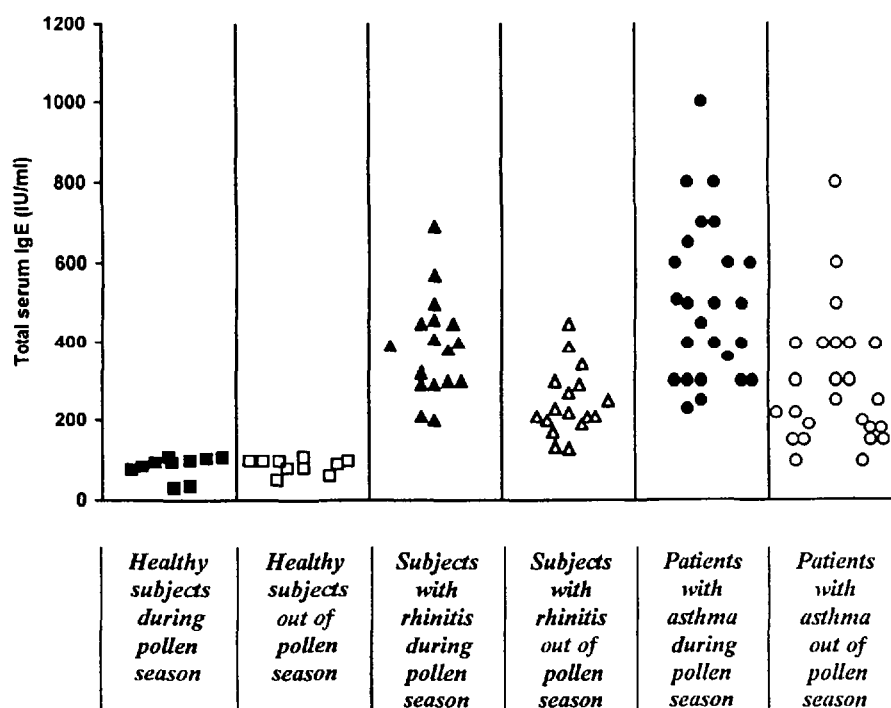


Figure 2. Individual values of total serum IgE in healthy subjects during (■) and out of (□) pollen season, in patients with rhinitis during (▲) and out of (△) pollen season, and in patients with asthma during (●) and out of (○) pollen season. During pollen season, mean $\pm$ SD of total serum IgE in healthy subjects was 87 ± 19 IU/mL, in patients with rhinitis was 388 ± 126 IU/mL, and in asthmatic patients was 498 ± 199 IU/mL. Out of the pollen season, mean $\pm$ SD of serum sCD23 in healthy subjects was 83 ± 29 IU/mL, in patients with rhinitis was 246 ± 86 IU/mL, and in asthmatic patients was 340 ± 153 IU/mL.

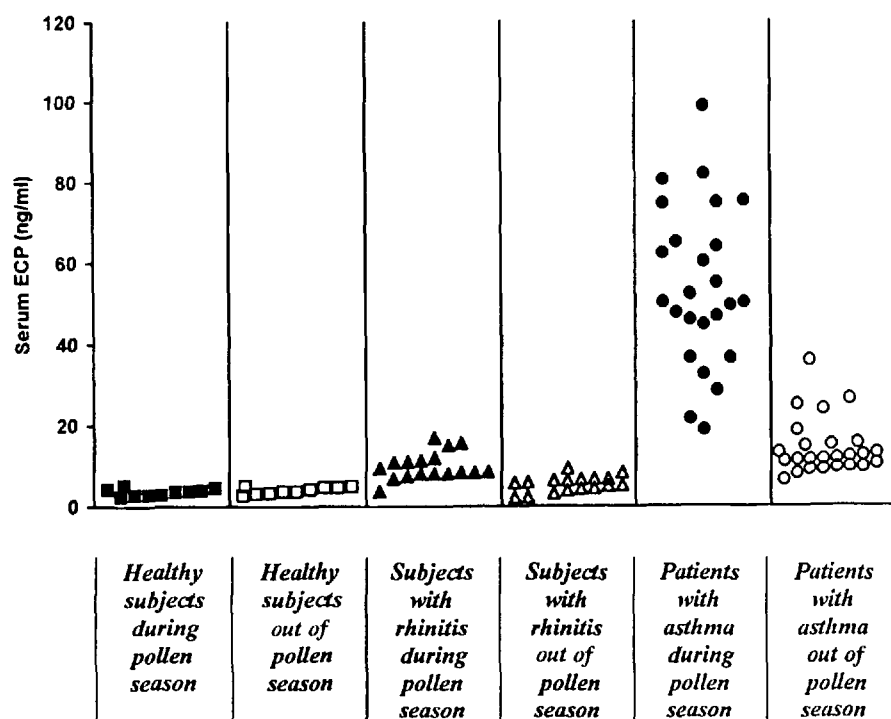


Figure 3. Individual values of serum ECP in healthy subjects during (■) and out of (□) pollen season, in patients with rhinitis during (▲) and out of (△) pollen season, and in patients with asthma during (●) and out of (○) pollen season. During pollen season, mean ± SD of serum ECP in healthy subjects was 4 ± 1 ng/mL, in patients with rhinitis was 10 ± 3 ng/mL, and in asthmatic patients was 54 ± 20 ng/mL. Out of pollen season, mean ± SD of serum ECP in healthy subjects was 3 ± 1 ng/mL, in patients with rhinitis was 5 ± 2 ng/mL, and in asthmatic patients was 12 ± 7 ng/mL.

versus 87 ± 19 IU/mL) ($p < 0.05$) and out of pollen season (340 ± 153 IU/mL versus 83 ± 29 IU/mL) ($p < 0.05$). Different from results obtained with sCD23, significant differences were observed between rhinitis patients out of pollen season and control subjects who displayed lower values (246 ± 86 IU/mL versus 83 ± 29 IU/mL) ($p < 0.05$).

As shown in Figure 3, a pattern completely different was observed by analyzing serum ECP levels because ECP levels were significantly increased only in asthmatic patients during pollen season. In fact, serum levels of ECP in asthmatic patients during pollen season (54 ± 20 ng/mL) were significantly higher than those observed in control subjects both during (4 ± 1 ng/mL) and out of pollen season (3 ± 1 ng/mL) ($p < 0.05$), in rhinitis patients both during (10 ± 3 ng/mL) and out of pollen season (5 ± 2 ng/mL), and in asthmatic patients (12 ± 7 ng/mL) ($p < 0.05$) out pollen season. No significant differences were observed among the remaining groups.

We also analyzed data from the asthmatic patients and from the subjects with rhinitis both during and out of pollen season for correlations between the levels of sCD23 and those of IgE and ECP. As shown in Fig. 4, in asthmatic patients, significant correlations were found between serum levels of sCD23 and those of total IgE both during (●, $r = 0.76$, $p < 0.01$) and out of (○, $r = 0.75$, $p < 0.01$) pollen season. In rhinitis patients, close correlations also existed between serum levels of sCD23 and those of total IgE both

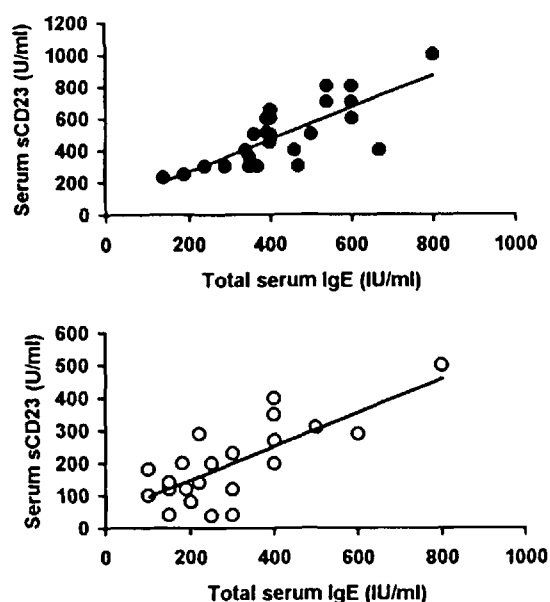


Figure 4. Correlation between serum sCD23 levels and total serum IgE during (●) and out of (○) pollen season, in asthmatic patients (respectively, $r = 0.76$, $p < 0.01$; $r = 0.75$, $p < 0.01$).

during (●, $r = 0.77$, $p < 0.01$) and out of (○, $r = 0.78$, $p < 0.01$) pollen season (Fig. 5). No significant correlations were observed between the levels of sCD23 and those of ECP (data not shown).

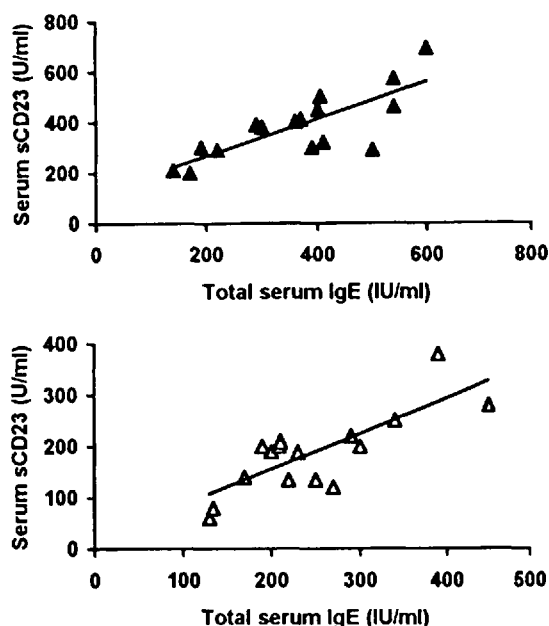


Figure 5. Correlation between serum sCD23 levels and total serum IgE during (▲) and out of (△) pollen season, in rhinitis patients (respectively, $r = 0.77$, $p < 0.01$; $r = 0.78$, $p < 0.01$).

DISCUSSION

The pathogenesis of allergic diseases is characterized by an increased synthesis of IgE, as a result of an interaction between B lymphocytes, Th-2 cytokines as IL-4 and IL-13, and sCD23.^{1,3,4,30–35} The aim of our work was to assess the pathophysiological role of sCD23. For this purpose, we have analyzed, blood values of sCD23, IgE, and ECP during and in patients allergic to *Parietaria*, during and out of pollen season.

Total serum IgE levels were clearly higher in atopic patients, as classically established.¹⁹ Concerning sCD23 serum levels, a similar pattern of results was obtained. Accordingly, significant correlations were shown between the levels of sCD23 and IgE in all groups of patients. A completely different pattern was observed by analyzing serum ECP levels because ECP levels were significantly increased only in asthmatic patient during pollen season. Accordingly, no significant correlations were observed between the levels of sCD23 and those of ECP.

In the present study, we have extended previous laboratory findings on ECP by demonstrating that natural allergen exposure induces an increase of ECP in asthmatic patients but not in rhinitis patients.^{20,29,36–38} Asthma and rhinitis are chronic inflammatory disorders of airways in which lymphocyte activation and the release of proinflammatory cytokines play a role.^{1–4,31} During the late-phase response, activated eosinophils are the predominant infiltrating cells at the mucosal sites.^{38–41} Several observations suggest that the quantification of ECP is, at present, the most informative marker of airway inflammation.^{20,36,38,40,42} The propensity of eosinophils to release ECP *in vitro* may be related to the extent to which the cells have been exposed to various

priming agents in circulation, such as different cytokines (i.e., IL-5, IL-8, RANTES) or mediators such as PAF and leukotrienes.^{20,35} Moreover, it is important to note that the major difference between upper and lower airways is in the surface area, which is around 150 cm² in the nose and several m² in the lower airways.⁴³

The close correlation between serum IgE and sCD23 is likely mediated by IL-4 because high levels of IgE *per se* do not increase serum levels. Modulation of CD23 expression by cytokines and the correlation of that modulation with IgE synthesis has been described. Accordingly, early studies demonstrated that elevated IgE levels were associated with elevated CD23 levels on B cells. The interest in CD23 upregulation has centered largely on IL-4, primarily because this cytokine directly causes both IgE production and CD23 upregulation by increasing CD23 synthesis rates. However, studies in humans have found that sCD23 potentiates IgE synthesis, although the manner is not known.^{6–9} Soluble CD23 can now be acknowledged as an important pleiotropic cytokine. In fact, culturing small, resting B lymphocytes with soluble CD23 molecules induces the synthesis of IgE *in vitro* when T cells are present. Particularly, IL-4 increases the precursor frequency of IgE-producing B cells, whereas sCD23 induces IgE-committed B cells to secrete relatively larger amounts of IgE.^{5–10} In several studies, the serum sCD23 levels have been reported to be elevated in atopic subjects, as compared to nonatopic subjects. Our results confirm these previous observations. Other studies, however, have not found a significant increase of sCD23 in atopic patients.^{5,14–18,44,45} These discrepant results might depend both on different study designs and on the large individual variability in serum levels of sCD23.¹⁷

However, present and previous results^{5,18} are consistent with a role for the pollen exposure in causing elevation of serum sCD23 levels in allergic patients. Concerning the mechanism(s) involved, inhalation of allergens has been demonstrated to result in the accumulation and activation of allergen-specific Th2-type T cells, which play a central role in the production of IL-4.^{46–48}

Identifying immune factors associated with the development of atopy can enhance our understanding of the *in vivo* mechanisms involved and may have utility in paradigms designed to prevent diseases. As demonstrated by the close correlation with total serum IgE values and the lack of correlation with serum ECP values, serum levels of sCD23 appear to be an additional marker for the diagnosis of atopy but not for the follow-up of allergic diseases.

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