

Expression of sCD23 in atopic and nonatopic blood donors: correlation with age, total serum IgE, and allergic symptoms

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Although structure, biologic activities, and expression of the low-affinity IgE receptor (Fc ϵ RII, CD23) have been investigated, the diagnostic value for allergies of this molecule and its soluble circulating fragment (sCD23) remains unclear. Therefore, serum sCD23 levels were measured in 203 blood donors. They were divided into atopic and nonatopic subjects by allergy history, physical findings of allergic symptoms, and corresponding specific circulating IgE antibodies. The group consisting of nonatopic subjects was divided into four age categories in order to exclude age-dependent variations in the expression of the low-affinity IgE receptor. In our study population, sCD23 serum levels were not influenced by age. Furthermore, no significant differences, especially no decrease in serum sCD23 levels, between the four nonatopic age groups were detected. There was no significant increase of sCD23 serum levels in atopic subjects in comparison with nonatopic blood donors. In addition, no correlation between total IgE levels and sCD23 serum levels could be detected, in either the group of atopic donors or the group of nonatopics. Our data suggest that the circulating low-affinity IgE receptor does not appear to be an additional general marker for the diagnosis of allergies, as previously suggested.

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The low-affinity IgE receptor (Fc ϵ RII or CD23) and its soluble circulating component (sCD23) have previously been characterized by cloning and sequencing techniques (12). The biologic activities and the cellular expression of this antigen are well known (6). CD23 is expressed on several different cells, including B and T cells, eosinophils, monocytes/macrophages, platelets, and Langerhans' cells (3, 4, 10, 11, 18). Its soluble circulating fragment, sCD23, is released by autocatalytic mechanisms (9, 14) and appears to be a disease maker for the hyper-IgE syndrome and for B-cell lymphoproliferate disorders; e.g., B-cell-derived chronic lymphocytic leukemia (17, 20). CD23 is considered to be a B-cell differentiation antigen, and some authors postulate that the expression of this antigen declines with age as a maker of impaired immune response (5, 23).

In patients suffering from allergic diseases, CD23 is overexpressed on monocytes and B cells (15, 19), with concomitant significant increases of sCD23 serum levels (13, 23). This overexpression of CD23 might play an important role in the pathogenesis

of atopic diseases by upregulating IgE synthesis (6). However, a clear correlation between IgE and sCD23 serum levels has not been found in every case (16).

We investigated whether total IgE levels in sera of atopic as well as in sera of nonatopic blood donors correlate with their serum sCD23 levels, and whether atopic subjects express significantly higher sCD23 serum levels than normal controls. sCD23 serum levels in patients with B-cell lymphoproliferate disorders were determined as a positive control group. For exclusion of an age-dependent influence in the expression of sCD23, especially a decrease, serum sCD23 levels of nonatopic blood donors were compared in age-matched groups.

Material and methods

Subjects

Serum IgE and specific IgE antibodies were measured in 850 blood donors. A careful history of allergy was taken, and physical examination for

allergic symptoms was done. Blood donors were defined as atopic subjects by the following criteria: a positive history and physical signs of atopy (i.e., hay fever, conjunctivitis, rash, gastrointestinal distress in relation to certain food), as well as a detectable corresponding specific IgE antibody. Increased total serum IgE levels (>100 kU/l) were not required to enter this group. Nonatopic blood donors were defined by the following factors: no history of allergy, lack of physical signs of allergic symptoms, negative specific IgE antibody screening tests (common aeroallergens as well as common food allergens), total IgE levels lower than 250 kU/l, and normal blood eosinophilia (less than 0.36/nl). According to this classification, only 100 blood donors could be clearly considered to be atopic and 103 to be nonatopic. Fourteen patients with B-cell lymphoproliferate disorders (e.g., B-CLL or non-Hodgkin's lymphoma (NHL)) participated in this study as an internal control group.

Methods

IgE measurement. Total IgE serum levels and circulating specific IgE antibodies in sera of blood donors were detected with the CAP IgE/CAP RAST fluoroimmunoassay (Pharmacia Biosystems, Freiburg, Germany). The determined values were expressed in kU/l. Common aeroallergens were measured with a multiscreen CAP RAST fluoroimmunoassay, including eight different allergens (sx1: weeds, grasses, trees, cat, dog, *Cladosporium*, and *Dermatophagoides*). Additionally, all sera were screened for six common food allergens (fx5: egg white, milk, flour, fish, peanuts, and soybean) with the CAP fluoroimmunoassay (Pharmacia Biosystems, Freiburg, Germany).

sCD23 serum levels were measured with a sandwich enzyme immunoassay (T-cell Sciences, Distribution Biermann), and the measured values were expressed in U/ml (1000 units is defined as the amount of released CD23 present in 1.0 ml of a concentrated T Cell Diagnostics, Inc. reference of supernatants from an EBV-transformed human B-cell line). The test principle is as follows. Polystyrene microtiter wells were precoated with an anti-CD23 monoclonal antibody (EBV TS/1 IgG1 mouse

antibody). Soluble CD23 in standards or patient's serum binds to coated antibodies, while the conjugated antibody (EBV, TS/2 IgG1 mouse antibody) binds to a second, distinct epitope on the CD23 molecule completing the sandwich. According to the information manual from the distributing company of this sandwich ELISA (T Cell Diagnostics), the sCD23 test kit does not detect any known cross-reactive antigens and is specific for sCD23. The company points out that elevated total serum IgE levels do not interfere with the performance of the sCD23 kit. The detection limit of the sCD23 ELISA is approximately 15 U/ml.

Eosinophils were measured by a counter (Coulter T-660, Coulter Electronics Limited GmbH, Krefeld, Germany), and a blood eosinophilia ≥ 0.36 /nl was considered to be increased (10).

Statistics

Mean values and standard error of means were calculated, as well as medians. Differences between the four age groups were analyzed with the Friedman test, which provides a two-way analysis of variance for nonparametric data (25). Correlation between nonatopic and atopic subjects was calculated with the Wilcoxon signed-rank test. Correlation between serum sCD23 and total IgE levels was also analyzed with the Wilcoxon signed-rank test (25).

Results

More than 850 blood donors entered this study. For establishment of a representative study population of atopic as well as nonatopic subjects the participants had to meet the following selection criteria: members of both groups must not suffer from acute infections, take any medication, or smoke in order to standardize obtained serum IgE levels. In addition to these criteria, only blood donors with a case history and physical findings of allergy, as well as detection of the corresponding specific IgE antibody, were regarded as atopic. Selection criteria for nonatopic subjects were the following: no family history of allergy, no physical findings of allergic symptoms, no expression of specific IgE antibodies, total IgE

Table 1. Average, standard deviation, and median of sCD23 serum levels in comparison between four different age groups. No significant differences between these groups were observed (NS: not significant; $P > 0.05$, Friedman test for nonparametric data)

	19–25 years 22.6 $\pm$ 2.1	26–35 years 30.2 $\pm$ 2.9	36–45 years 40.5 $\pm$ 2.8	45–60 years 52.7 $\pm$ 3.4	Significance
sCD23 mean (STD)	233.74 U/ml $\pm$ 300.4	212.8 U/ml $\pm$ 230.5	227.38 U/ml $\pm$ 325.8	230.7 U/ml $\pm$ 257.4	NS
sCD23 median	125.5 U/ml	97.95 U/ml	116.1 U/ml	100.2 U/ml	NS

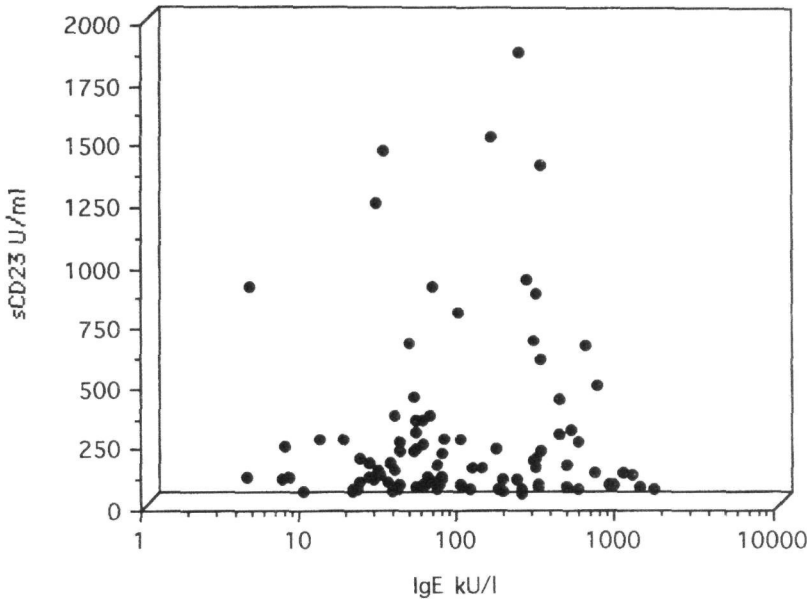


Fig. 1. Comparison of total IgE and sCD23 serum levels in sera of atopic subjects (*n* = 100). There was no correlation between these two variables (Wilcoxon signed-rank test).

levels less than 250 kU/l, no signs of contact allergies, and normal eosinophilia. After consideration of all these requirements, only 100 blood donors could be clearly identified as atopic and 103 as nonatopic subjects.

For exclusion of an age-dependent influence on the expression of serum sCD23 levels, nonatopic blood donors were divided into the following four age groups: 19–25 years (mean 22.5 ± 2), 26–35 (mean 30 ± 2.9), 36–45 (mean 40.5 ± 3), and 46–60 (mean 52.7 ± 3.4). No significant differences (*P* > 0.05) in serum sCD23 concentrations were observed in our study population. In particular, no decrease in serum sCD23 levels with increasing age was detected (Table 1).

Total IgE serum levels of atopic subjects in relation to their sCD23 serum levels are shown in Fig. 1.

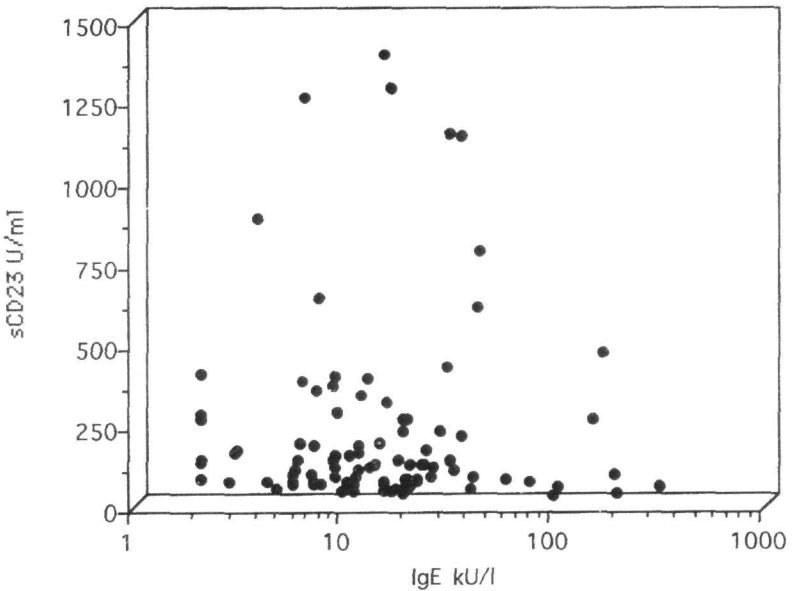


Fig. 2. Relation of serum levels of total IgE and sCD23 in sera of nonatopic subjects (*n* = 103). No correlation between these two variables was detected (Wilcoxon signed-rank test).

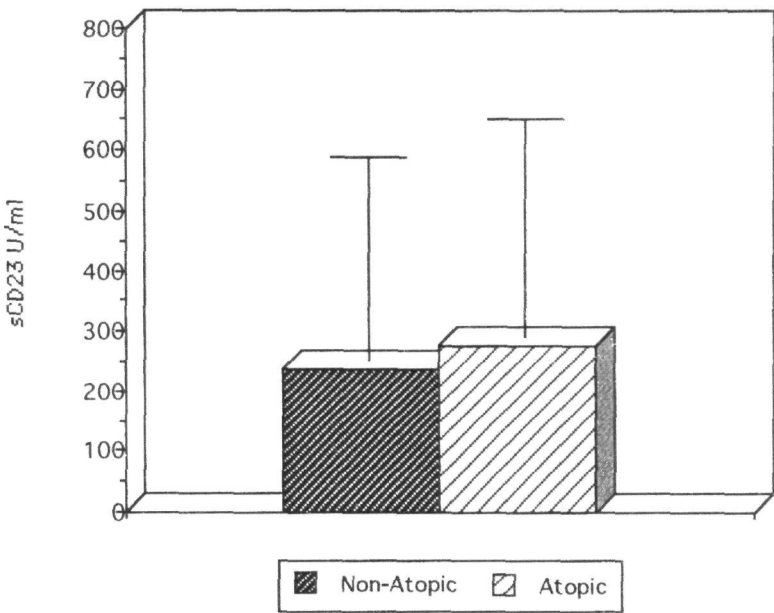


Fig. 3. Comparison between sCD23 serum levels in atopic and nonatopic subjects. No significant differences between these two groups were detected.

There was no correlation between these two variables. The comparison between sCD23 and total serum IgE in nonatopics is shown in Fig. 2. Again, no correlation between serum IgE and sCD23 was detected.

Serum sCD23 concentrations in the sera of nonatopic subjects in comparison with atopic blood donors are shown in Fig. 3. sCD23 concentrations tended to be higher in atopic subjects, but analysis of the data by the Wilcoxon test showed sCD23 serum values not to be significantly different between the two groups. sCD23 serum levels in the 14 patients with B-cell lymphoproliferate disorders (B-CLL and NHL) were clearly increased over sCD23 levels of nonatopic and atopic participants in this study and served as an internal positive control group (Table 2).

Discussion

Increased total IgE protein levels are associated with atopic diseases as well as with neoplasms, immunodeficiencies, and viral and parasitic infections (24). However, reference values for total IgE serum concentrations are difficult to establish because of environmental factors such as age, race, sex, and smoking habits (1, 7, 22). Differences in serum IgE levels

Table 2. Average, standard deviation, and median of sCD23 serum levels in atopic and nonatopic subjects and patients with B-cell lymphoproliferate disorders

	Nonatopic	Atopic	Patients (B-CLL, NHL)
sCD23 average (STD)	235.5 U/ml ±322.6	273.2 U/ml ±390	1309 U/ml ±371.1
Median	116.9 U/ml	135 U/ml	1272 U/ml

may even vary from country to country (8). Therefore, additional variables appear to be necessary for the diagnosis and the follow-up of patients with allergic diseases. Such variables should meet the following criteria in order to be suitable for clinical practice: they should be easy to measure, reliable, and reproducible. Serum level of sCD23, which plays an important role in the regulation of the IgE synthesis (21), appears to be a suitable variable in view of the availability of different monoclonal antibodies and enzyme immunoassays.

Several studies have been published on sCD23 serum levels in atopic subjects, as compared with levels of nonatopic subjects (6, 13, 15, 23). The results suggest that increased sCD23 serum levels in atopic subjects refer to increased IgE synthesis. However, our results do not agree with previous reports. We did not find significantly increased sCD23 levels in atopic blood donors in relation to nonatopic subjects. This discrepancy might be explained by different study designs. In all previous studies, the group of atopic subjects was defined as having at least four features: skin reactivity to common aeroallergens, family history, case history, and increased total IgE concentration. Subjects who had the first three features of allergy, but who expressed IgE levels lower than 200 kU/l were excluded from the investigation. In our study, increased IgE levels represented no selection criteria for the definition of allergic subjects. Our latest investigation detected that approximately 30% of all diagnosed atopic subjects in a study population of 1088 blood donors expressed total IgE levels below 100 kU/l (unpublished data). In our opinion, this percentage appears far too large to justify a serum IgE level larger than 200 kU/l as a selection criterion for the group of atopic subjects.

Our results also differ in another aspect from previous reports. We did not find age-related differences in the expression of sCD23 serum levels in our study population. Therefore, we did not compare the atopic with the nonatopic group in an age-matched manner. The cause of these contradictory results might be the large individual variability in serum levels of this antigen. Larger numbers of participating nonatopic subjects seem to be necessary for the evaluation of this problem. On the other hand, our age range of 18–60 years might not be large enough to detect these differences. Furthermore, little is known about environmental influences, such as seasonal variations, on serum sCD23 levels. Longitudinal studies seem to be necessary to learn more about the expression and variation of the circulating low-affinity IgE receptor.

Although sCD23 plays an important role in the regulation of the IgE synthesis, no correlation between the two variables was detected either in pre-

vious investigations (6, 16) or in our study. An explanation for these interesting findings might derive from the observation that after bone marrow transplantation sCD23 appears first in the serum of the patient, followed by IgE after several days (2). This delayed appearance of IgE could possibly explain the lack of concomitant augmentation of sCD23 and IgE.

We conclude that further studies are necessary to investigate the variability of the circulating low-affinity IgE receptor before this antigen can be considered to be a valuable additional marker for the diagnosis of allergic diseases.

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