

Serum levels of sCD23 and sCD25 in children with asthma and in healthy controls*

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To investigate whether markers of lymphocyte activation are useful markers of disease activity in childhood asthma, we studied serum levels of soluble CD25 (receptor for IL-2) and soluble CD23 (low-affinity receptor for IgE) in 178 children (aged 2–18 years) suffering from mild to moderate asthma (mean asthma severity score: 2, range: 1–4), and in 175 healthy age-matched controls. Levels of sCD23 and sCD25 were inversely related to age. sCD23 was lower in patients with asthma (means per age group: 4.93–2.29 µg/l; controls: 6.92–4.11 µg/l, $P < 0.05$), while sCD25 tended to be higher (1601–597 kU/ml, controls: 1350–661 kU/ml, $P = \text{NS}$). sCD25 correlated significantly with asthma severity score ($r = 0.41$; $P < 0.01$) and MEF₂₅ (maximum expiratory flow at 25% of vital capacity, $r = -0.43$; $P < 0.05$) in children < 10 years, while sCD23 correlated with asthma severity ($r = 0.28$; $P < 0.05$) in children > 10 years. On follow-up, levels of sCD25 normalized with clinical improvement. In children with nonatopic asthma, levels of sCD25 were significantly higher than in atopic patients. Our observations provide further evidence of the role of T-cell activation in asthma. Monitoring of lymphocyte activation markers, particularly levels of sCD25, may be useful in the follow-up of asthmatic children.

From both clinical and experimental evidence, asthma is now viewed as an inflammatory airway disease involving lymphocyte activation and the release of proinflammatory cytokines (3, 9, 10, 15, 20, 24, 27). Lymphocytes express various surface markers upon activation. These include CD25; the IL-2-receptor α -chain; a 55-kDa surface molecule on T cells (19, 21) and, to a minor extent, on B cells (7); and CD23, the 45-kDa, low-affinity receptor for IgE (Fc $_{\epsilon}$ RII), which is mainly expressed by activated B cells, but which may be expressed by T cells, monocytes, and eosinophils as well (4, 5, 28). Components of both surface antigens are released upon activation (soluble CD25, sCD25; soluble CD23, sCD23) (19, 28) and can be measured in serum and other body fluids. Serum levels of sCD25 and sCD23 correlate closely with the number of activated CD25⁺ T cells (in the peripheral blood and bronchial mucosa) (9, 19) and the number of activated CD23⁺ B cells (4,

17), respectively. Increased levels of sCD25 or sCD23 have been observed in various immunologically mediated disorders such as rheumatoid arthritis (13, 23), renal graft rejection (22), and atopic diseases (8, 28). Both molecules are involved in immunoregulation: while sCD25 competes with the surface IL-2-receptor for IL-2 (21), sCD23 is involved in the regulation of IgE synthesis (4, 5, 28). The expression of CD23 (4, 5) and CD25 (7) is promoted by IL-4. In asthmatic subjects, surface expression of CD25 on peripheral lymphocytes (9, 10, 25) and on lymphocytes obtained by bronchial lavage (3, 27) is increased. Previous studies in adults with asthma have shown elevated levels of sCD25 (6, 9, 20); a correlation with disease activity was found in some (9, 20, 24) but not all studies (6).

Assessment of immune activation is of potential value in monitoring patients with bronchial asthma. No information is available so far on the significance of activation markers in children. We therefore studied levels of sCD25 and sCD23 in asthmatic children and in healthy age-matched controls.

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Material and methods

Patients and controls

A total of 178 children (125 boys, 53 girls), aged 2–18 years, with a history of recurrent airway obstruction of at least 6 months' duration were studied. Diagnosis of bronchial asthma was established according to criteria of the American Thoracic Society (2). Body plethysmography was performed in children > 5 years (Jaeger Bodyscreen, Würzburg, Germany). Of our patients, 90% had a positive individual or family history of atopic disorders. Their mean serum IgE was 465 kU/l (median: 280; range: 1–4119 kU/l). Seventeen patients (9%) were suffering from nonatopic asthma, which was triggered by infections or exertion, and characterized by the absence of allergen-related symptoms, normal IgE (mean serum IgE: 22 kU/l; median: 21, range: 3–59 kU/l), and a negative RAST to seven common, inhaled allergens. All patients were assigned a severity score of 1–4 based on clinical data (frequency and severity of symptoms) and lung function variables ((1); with modifications (12)). The median score of our patients was 2.0 (range, 1–4; grade 1: 27.9%, grade 2: 53.1%, grade 3: 17.7%, and grade 4: 1.4%). Levels of sCD23 and sCD25 were correlated with

the asthma severity score and lung function variables reflecting broncho-obstruction; namely, FEV₁ (forced expiratory volume in 1 s, median: 83.0% of predicted, range: 18–103) and MEF₂₅ (maximum expiratory flow at 25% of vital capacity, median: 47% of predicted, range: 9–125). Patients were treated with inhaled sodium cromoglycate, β_2 -agonists, oral theophylline or inhaled budesonide.

A total of 175 children presenting to the outpatient clinic for preoperative evaluation or evaluation of presumed growth disorders served as age-matched controls. Children with a known history of allergies or elevated IgE (> 100 kU/l) were excluded. Serum samples were taken – with informed parental consent – for routine laboratory investigations.

Assay for soluble CD23

Serum levels of sCD23 were determined by a solid-phase ELISA with monoclonal murine antihuman anti-sCD23 as the first, sheep antihuman sCD23 as the second, and horseradish-peroxidase-coupled porcine antish sheep IgG as the third antibody (Binding Site Ltd, Birmingham, UK). Samples were run in duplicate. Results were read at 450 nm (Dynatech Elisa photometer) and expressed in μ g/l. The lower detection limit was 1.0 μ g/l. The coefficient for intra-assay variation was 7%; for interassay variation, 9%.

Assay for soluble CD25

Serum levels of sCD25 were determined similarly with a monoclonal murine antihuman anti-sCD25 (T-Cell Sciences, Cambridge, MA, USA). Samples were run in duplicate. Results were read at 492 nm and expressed in U/ml (1000 U is equivalent to the amount of sCD25 present in 1.0 ml supernatant of PHA-stimulated reference lymphocytes). The detection limit was approximately 50 U/ml sCD25. The intra- and interassay coefficients of variation were 3 and 5%, respectively.

Statistical analysis

For statistical analysis, the chi-square test, Student's t-test, and Wilcoxon's test for pair differences were used as indicated in the text.

Results

Soluble CD23 in children with asthma and in healthy controls

The sCD23 levels in children with asthma and in healthy age-matched controls are given in Fig. 1. Levels of sCD23 decreased with age in both groups. Mean levels tended to be lower in asthmatic chil-

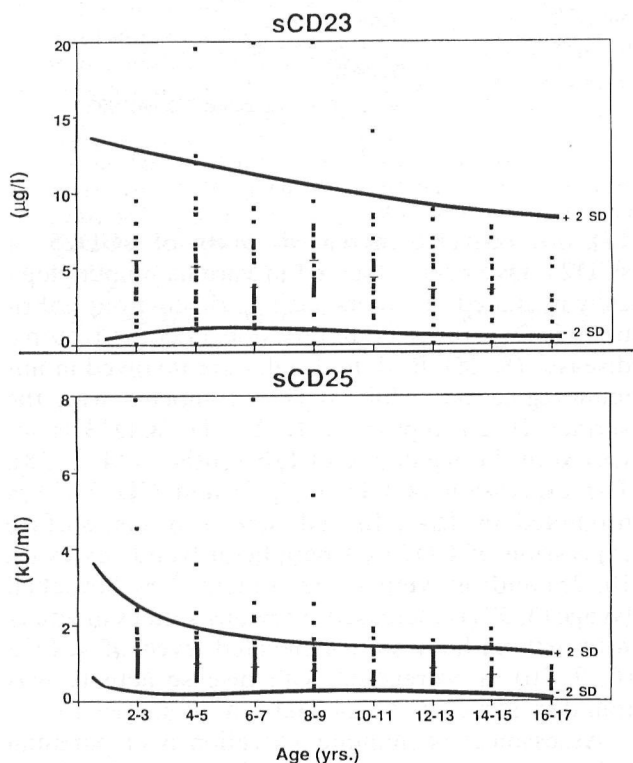


Fig. 1. Age-dependent serum levels of sCD23 and sCD25 in asthmatic children, as compared with normal controls. Individual patient data ($n = 178$) and medians (—). Lines denote upper and lower limits of normal levels (± 2 SD) derived from healthy controls ($n = 175$).

dren; this difference was significant ($P < 0.05$) in the age groups 24–48 months (4.93 ± 3.07 and $6.92 \pm 2.97 \mu\text{g/ml}$) and 17–18 years (2.29 ± 1.90 and $4.11 \pm 1.94 \mu\text{g/ml}$). Mean levels of sCD23 correlated with IgE (overall correlation coefficient $r = 0.10$; $P = 0.185$); this correlation was significant ($P < 0.05$) at ages 2–3 ($r = 0.41$) and 14–15 years ($r = 0.45$). A significant correlation between levels of sCD23 and asthma severity score (Fig. 2) was found in older children (> 10 years), whereas FEV_1 ($r = -0.17$) and MEF_{25} ($r = -0.18$) correlated only weakly ($P > 0.23$). In younger children, an inverse relationship between sCD23 and severity score, FEV_1 ($r = 0.40$), and MEF_{25} ($r = 0.30$) was observed ($P = \text{NS}$).

Soluble CD25 in children with asthma and in healthy controls

Levels of sCD25 decreased with age in both groups (Fig. 1). They tended to be higher in asthmatic children ($P = \text{NS}$). sCD25 did not correlate with IgE ($r = 0.04$; $P = 0.866$). Levels of sCD25 correlated with asthma severity score (Fig. 2), MEF_{25} ($r = -0.43$; $P = 0.048$), and FEV_1 ($r = -0.31$; $P = 0.162$) in younger children, whereas in children ≥ 10 years, no correlation between lung function variables and levels of sCD25 ($r = -0.08$ – 0.14 ; $P > 0.35$) was found.

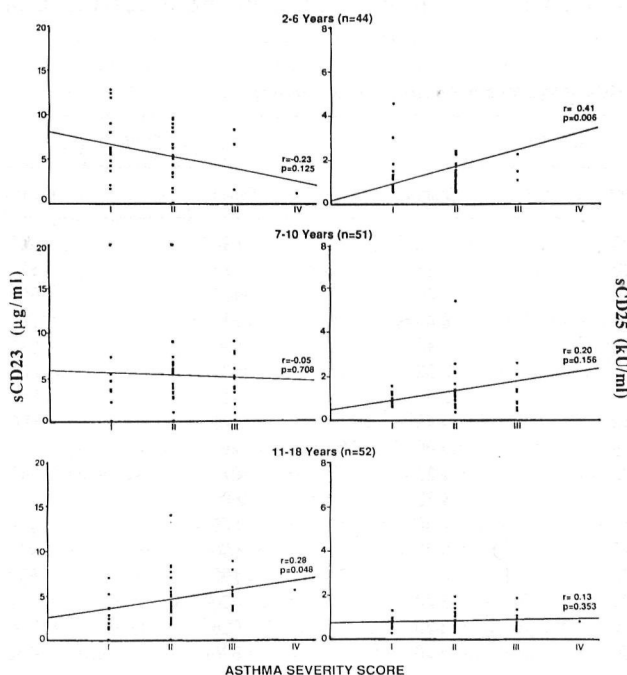


Fig. 2. Correlation of asthma severity score with sCD23 and sCD25.

Follow-up investigations

Information about follow-up examinations, including lung function and determination of sCD23 and sCD25, was available for 14 patients (Table 1). The median period between both visits was 10 months (range: 5–30 months). Levels of sCD25, but not sCD23, correlated significantly with improvement of the asthma severity score on follow-up ($P < 0.01$).

sCD23 and sCD25 in children with nonatopic asthma

Seventeen patients with nonatopic asthma were compared with 17 patients matched for age and asthma severity who were suffering from atopic asthma (Table 2). The nonatopic patients revealed significantly higher levels of sCD25 ($P < 0.05$), whereas the levels of sCD23 did not differ significantly between both groups.

Discussion

Activated lymphocytes contribute to the pathogenesis of asthma. The present study was done to assess serum levels of two soluble lymphocyte activation markers, sCD23 and sCD25, in children with asthma and to correlate them with disease activity. We observed lower levels of sCD23 and slightly higher levels of sCD25 in children with asthma than in healthy age-matched controls. Disease activity was found to correlate with sCD25 in younger children, and with sCD23 in older children.

Our findings confirm and extend previous observations on the role of lymphocyte activation in the pathogenesis of asthma. The inverse correlation between age and levels of sCD25 and sCD23 (Fig. 1) is thought to reflect the physiologic decrease of absolute numbers of T and B lymphocytes with age (11), as well as maturational changes of lymphocyte activation (16). The observation of a positive correlation between sCD25 and activity of bronchial asthma in children < 10 years (Fig. 2) points to the preeminent role of inflammatory triggers in younger children with asthma (15). In adult patients with asthma, indicators of T-cell activation such as release of $\text{IFN-}\gamma$ or sCD25 have been reported to correlate with disease activity by some (9, 20, 24), but not all (6) studies. However, age, duration, and severity of disease, as well as different treatment modalities, render a direct comparison between adult and pediatric asthma patients difficult.

Significantly higher levels of sCD25 were noted in children with nonatopic asthma than in atopic asthma (Table 2). The number of activated CD4^+ cells was recently reported to be higher in nonatopic asthma patients (9, 26), and a significant correlation between sCD25 and FEV_1 could be observed only

Table 1. Follow-up investigations of sCD23 and sCD25 levels in 14 children with asthma

Pat. no.	Age (y, m)	Asthma severity score		sCD23* ($\mu\text{g/l}$)		sCD25** (U/ml)	
		1st	2nd	1st	2nd	1st	2nd
1	33 m	3	2	6.70	5.80	1460	1260
2	46 m	4	3	1.25	1.00	8350	1400
3	56 m	3	2	1.00	2.60	1400	710
4	7 y 10 m	3	2	5.55	9.40	1405	990
5	8 y 6 m	3	2	20.00	20.00	1400	1210
6	8 y 8 m	2	1	nd	nd	990	455
7	9 y 1 m	3	2	5.20	1.70	2105	645
8	9 y 11 m	2	1	3.25	2.80	610	540
9	10 y	3	2	nd	nd	460	335
10	10 y 11 m	3	2	8.40	2.65	1933	980
11	12 y 6 m	2	1	5.80	3.60	850	1470
12	12 y 9 m	2	1	3.40	0	560	560
13	13 y 2 m	3	2	3.85	5.10	1150	690
14	14 y 8 m	3	2	7.60	2.40	865	430

Pat. no.=patient number, y=year, m=month, 1st=first visit, 2nd=follow-up visit, nd=not done.

Wilcoxon test for pair differences: *sCD23: T=58, *P*=nonsignificant; **sCD25: T=10, *P*<0.01.

in this subgroup (20). Severe and prolonged broncho-obstructive reactions to inflammatory stimuli are typical of patients with nonatopic asthma. Among their T-cell populations Th-1 cells were found to predominate (26), resulting in elevated levels of IL-2 and subsequently increased T-cell activation.

Levels of sCD23 have previously been shown to decrease with age (14, 17) and to correlate with serum IgE (17, 28). In accordance with our study, no significant difference between atopic and nonatopic patients was reported in children > 2 years of age (17). In contrast to sCD25, sCD23 correlated with asthma severity and individual lung function varia-

bles in older children (> 10 years) only. The reasons for this difference are presently unknown. It might be attributed to a relative increase of CD23⁺ B cells with age (11) or higher serum concentrations of IgE (28). Study of age-related levels of, or response to, circulating IL-4 might help to elucidate the age-dependence of sCD23 levels.

Although their significance for the pathogenesis of asthma is still unknown, these molecules may be helpful in the monitoring of asthma or other diseases involving lymphocyte activation (8, 13, 22, 23, 28). Our results suggest that in patients with asthma, sCD25 may be more helpful in the assessment of

Table 2. Levels of sCD23 and sCD25 in children with nonatopic asthma and in children with atopic asthma matched for age and asthma severity

Pat. no.	Age (y, m)	Asthma severity score	sCD23* ($\mu\text{g/l}$)		sCD25** (U/ml)	
			Patient	Control	Patient	Control
1	31 m	2	5.63	0	680	840
2	33 m	2	5.10	3.45	1535	920
3	33 m	3	6.70	3.00	1460	1350
4	46 m	4	1.25	8.40	8350	1080
5	60 m	1	5.60	2.45	3050	990
6	60 m	2	5.80	9.03	1460	880
7	62 m	2	0	2.10	1410	820
8	67 m	2	4.43	1.40	720	560
9	68 m	2	13.25	9.00	1250	1160
10	6 y 6 m	2	9.05	3.85	1075	940
11	10 y	2	2.60	4.80	1685	460
12	10 y 3 m	2	3.40	4.90	605	470
13	12 y 5 m	2	3.40	3.72	560	475
14	13 y 10 m	2	5.80	0	700	690
15	14 y 2 m	3	4.90	3.80	430	550
16	16 y 2 m	2	5.00	2.80	605	805
17	17 y 10 m	4	5.70	2.20	820	400

y=year, m=month.

Wilcoxon test for differences between nonatopic and matched atopic asthma patients: *sCD23: T=40.5, nonsignificant; **sCD25: T=23.5, *P*<0.05.

disease activity than sCD23. On the other hand, sCD23 is potentially useful in the early diagnosis of atopic disorders (18). However, because of overlap of mean serum levels between asthmatic and healthy children, repeated monitoring of these indicators appears to be more informative than single determinations (Table 1). With regard to the decrease of both sCD23 and sCD25 levels with age, age-adjusted reference values have to be taken into account for the interpretation of both variables. Although serum levels of sCD23 and sCD25 were shown to correlate with the total number of lymphocytes expressing CD23 or CD25 (6, 14, 16), it has to be stressed that without direct analysis of surface-bound CD23 and CD25, the differential contribution of T and B cells or monocytes, respectively, to the amount of soluble CD23 and CD25 measured in serum or secretions can be estimated only roughly. Future studies should determine the usefulness of monitoring sCD25 and/or sCD23 levels in individual patients with bronchial asthma for the prediction of imminent broncho-obstruction and the delineation of disease subgroups.

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