

Serum levels of the soluble low affinity receptor for IgE and soluble interleukin-2 receptor in childhood, and their relation to age, gender, atopy and allergic disease

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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 disease. Two candidates suggested for such roles are the soluble low affinity receptor for IgE (sCD23) and the soluble interleukin-2 receptor (sCD25). To assess serum levels of these factors blood samples were collected at birth and at age 6 in a large nonselected population from Tucson, AZ. Log mean sCD23 and sCD25 levels decreased from birth to age 6, (for sCD23 0.60 ffi 0.26pg/l, n=340 and 0.53 + 0.28pg/l, n=333 and for sCD25 1.95 i 0.14pM, n=304 and 1.86 ffi 0.20pM, n=327, for the two ages respectively. Anglo children had lower sCD23 levels at birth compared to Hispanic children ($p < 0.01$); no effect of gender was observed. Skin test reactivity at age 6 was directly related to sCD25 levels at age 6 ($p = 0.007$) and even levels at birth showed a similar trend ($p = 0.06$). These relations were distinct from any relation to total serum IgE. No relation was observed with sCD23 levels for either skin test reactivity or serum IgE. The prevalences of asthma, rhinitis and eczema by age 6 were unrelated to sCD25 or sCD23 levels. The results indicate that soluble CD23 and CD25 have higher levels at birth than later in childhood and that the development of skin test reactivity may be associated with regulatory mechanisms involving sCD25, whereas sCD23 was not similarly implicated.

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Elevated total serum IgE is a common characteristic in asthma, allergic rhinitis and eczema. Serum IgE levels at birth are very low, approximately 300 fold less than adult IgE levels (1–3). Longitudinal studies suggest increases in IgE levels occur prior to the onset of atopic disease but the predictive capacity of IgE levels at birth for later allergy is controversial (4, 5). It is possible that factors involved in regulating IgE synthesis may better serve as predictive indicators for atopy early in life and would thus have important clinical implications for the prevention and/or early treatment of future atopic disease.

One such factor is the low affinity IgE receptor (FCεRII, CD23) present on B cells and upregulated when B cells commit to IgE synthesis (6). In atopic patients CD23 is overexpressed on B cells and

monocytes (7). When CD23 is up-regulated on B cells, it is accompanied by receptor associated autolytic cleavage and release of soluble CD23 (sCD23) from the membrane bound CD23 (8–11). A few recent studies have suggested that blood levels of sCD23 may serve as a marker (12–16) or even a predictive indicator of atopic disease but relationships were seen only in occasional age-specific subgroups.

In addition to sCD23, serum levels of another marker, the soluble interleukin-2 receptor (sIL-2R, sCD25) have been reported to be significantly elevated in subjects with atopic dermatitis (17), asthma (18) and asthma severity (19, 20), as compared to normal control groups. Moreover, Walker et al. reported a high correlation between the degree of air-

way obstruction in asthma, the number of peripheral T lymphocytes expressing CD25 and the concentration of sCD25 (21). This marker has been shown to be a soluble form of the alpha chain of the IL-2 receptor (22).

The studies suggesting associations between sCD23 and sCD25 and atopy have used relatively small and/or selected patient populations. In the present study we have used a large unselected population to examine the capacity of cord serum levels of sCD23 and sCD25 to serve as predictive indicators of future atopy, allergic disease and/or serum IgE at age 6. We have also examined whether soluble levels of these markers at age 6 are associated with concomitant allergic markers and/or symptoms.

Material and methods

Population and samples

Healthy neonates born between May 1980 and October 1984 whose parents were members of a large Health Maintenance Organization in Tucson, Arizona were eligible for enrollment in the Children's Respiratory Study (CRS), a longitudinal study of respiratory health in children (23). A total of 1246 infants were enrolled without selection as to respiratory symptoms.

Parents of enrolled children completed health questionnaires at regular intervals during the study. Parental history of smoking, ethnicity and maternal education were determined from responses on the enrollment questionnaire. Information on physician diagnosed eczema occurring during the first year of life was obtained from the questionnaire completed during the infants' second year of life (mean age 1.6 year, SD=0.35). Physician diagnosed asthma or rhinitis at age 6 and any parental report of eczema in the child in the first 6 years was determined from the health questionnaire completed when the child was 6 years old (mean age 6.4 years, SD=0.5).

The diagnosis of active allergic rhinitis included a parental affirmative to the question 'Has your child ever had hay fever or any other condition that makes your child's nose stuffy, itchy or runny apart from colds?', a physician confirmation that the 'symptoms were due to allergies', and a parental report that the symptoms were 'still present' at the time the questionnaire was completed. Those children whose rhinitis was not 'still present' at the time of the questionnaire, who had non-allergic rhinitis or who did not see a physician for their symptoms were included with the no rhinitis group.

Physician diagnosed active asthma included a 'yes' answer to 'Has your child ever had asthma (reactive airways disease)?', an age at which the physician diagnosed the child with asthma and a parental

report of "asthma attacks or episodes" during the previous year.

Active wheeze during the past year included a 'yes' answer to 'Has this child's chest ever sounded wheezy or whistling?' and a report of wheezing during the past year. If a child was diagnosed with asthma and the parent did not report an asthma attack or episode during the previous year but did report active wheezing, the child was considered an active asthmatic. Children without asthmatic attacks/episodes or wheezing during the previous year were categorized as inactive asthmatics and included with the non-asthmatic group.

For analyses, children were categorized into allergic disease groups in relation to the presence of asthma and rhinitis. This categorization created 4 allergic disease groups, including 1) asthma, no rhinitis 2) rhinitis, no asthma 3) both asthma and rhinitis and 4) a control group without asthma or rhinitis.

Sera from umbilical cord blood samples collected at birth and peripheral blood samples collected from healthy subjects at age 6 were stored at -70°C. Of the 1246 children enrolled in the study, 434 had sufficient quantities of cord and/or year 6 sera for assaying either sCD23 or sCD25 or both. Levels of sCD23 were measured in 340 cord samples and 333 year 6 samples, including 250 matched samples. Levels of sCD25 were measured in 304 cord samples and 327 year 6 serum samples, including 221 matched samples. Overall there were 210 children with all four determinations. Total serum IgE levels were determined in 433 cord blood samples and 430 age 6 blood samples.

Of the 434 children included in this study, 49.7% were girls. For analyses, ethnicity was divided into two groups, those infants with at least one anglo parent (83%) and those with non-Anglo parents (17%). Of the latter, 80% had Hispanic parents.

Informed consent was obtained from the parents of participating subjects and the study was approved by the College of Medicine Human Subjects Committee of the University of Arizona.

Maternal/cord Study

A small study was initially conducted to evidence that maternal levels of sCD23 crossed the placenta. Eighteen paired maternal and cord samples were evaluated. These samples were derived from military dependents hospitalized for childbirth at the USAF Hospital, Davis-Monthan Air Force Base.

Soluble CD23 and CD25 Levels in Serum

Commercial ELISA kits from The Binding Site (Birmingham, UK) and AMAC Inc. (Westbrook, Maine) were purchased to measure sCD23 and sCD25, re-

spectively. Both assays were used according to the manufacturer's instructions. The mean and standard deviation (SD) sCD23 level for control serum supplied was 9.72 $\pm$ 0.85 pg/L. Kit control values achieved from our eight sCD23 assays yielded a mean value of 9.54 $\pm$ 1.33 μ g/L (SD). The coefficient of variation for sCD23 intra and inter-assay variation were 7.5% and 8.5% respectively. For sCD25 no manufacturer controls were supplied. We prepared a control derived from pooled neonatal cord samples which was aliquoted and frozen. The mean value for this control was 96.4 pM $\pm$ 14.5 pM (SD) (IpM=42ng/l). The coefficient of variation for sCD25 intra and inter-assay variation were 8.5% and 8.9% respectively. Most (93%) samples and all standards and controls were analyzed in duplicate. All samples were run undiluted.

Serum IgE levels

Serum IgE levels were assayed by Phadebas Radio-immunosorbent Test (PRIST) using commercially available kits (Pharmacia Diagnostics, Piscataway, NJ) as previously described (2). At age 6, peripheral blood samples for total serum IgE determinations were drawn from 99.1% of participating children (n=430/434). These samples were collected between 4.4 and 9.8 years of age. Some children refused phlebotomy. IgE levels were unrelated to collection age (median age 6.2yr). All samples were assayed in duplicate and results expressed as IU/ml.

Alleras skin tests

Extracts of 7 common aeroallergens in the Tucson area and diluents were obtained from Hollister-Stier Laboratories (Everett, Washington): house dust mix (1:10w/v), *Alternaria alternata* (1:100w/v), bermuda grass (1:20w/v), careless weed (1:20w/v), and olive, mesquite and mulberry trees (1:20w/v). Allergy skin prick tests were performed at age 6 in 98.6% (n=428/431) of the children (except mulberry tree antigen, which was applied to 410 subjects). Tests were read at 20 min and the sizes of the wheals elicited by each allergen were recorded as the sum of the 2 diameters at right angles to each other (in mm). Wheal sizes of 3mm or more were considered positive.

Statistical methods

Statistical analyses were performed using the Statistical Package for the Social Sciences for UNIX, version 4 (SPSS Inc. Chicago, Ill.). Both cord and age 6 sCD23 values are log-normally distributed and results are expressed as geometric mean values in pg/l. Similarly, both cord and age 6 sCD25 values are

log-normally distributed and results are expressed as geometric mean values in pM. Total serum IgE values are log-normally distributed and results are expressed as geometric mean values in IU/ml. Statistical analyses involving these variables were performed using standard parametric techniques. The number of positive skin tests was used as the percent of group with one or more positive test and analyzed nonparametrically with trend chi-square. A p-value < 0.05 (two-tailed) was considered statistically significant for all tests.

Results

The frequency distributions of sCD23 and sCD25 levels in umbilical cord serum and age 6 serum are illustrated in Fig 1. All samples tested had detectable levels of each marker. Geometric mean sCD23 levels were significantly higher at birth (3.8 pg/l, n=340, 95%CI: 3.5-4.2) compared to age 6 (3.4 Mg/l, n=333, 95%CI: 3.2-3.7; p<0.01). Geometric mean sCD25 levels were also significantly higher at birth (89.0 pM, n=304, 95tCI: 85.892.3) compared to age 6 (72.1 pM, n=327, 95%CI: 68.5-75.8; p<0.001).

Paired cord and age 6 sCD23 values were significantly correlated (r=0.12, n=250, p=0.05) as were paired sCD25 values (r=0.26, n=221, p=0.001) demonstrating a significant tendency for the levels of each marker to track with age. In cord sera, levels of sCD23 were not significantly correlated with sCD25 levels. At age 6, however, levels of sCD23 and sCD25 showed a modest correlation (r=0.15, n=313, p=0.008).

No effect of gender, parental smoking, or maternal education on either sCD23 or sCD25 at birth or age 6 was observed. Geometric mean sCD23 levels at birth were lower in those infants with at least one Anglo parent, (3.8 μ g/l, n=284, 95%CI:3.5-4.1) compared to those with non-Anglo parents (4.9 Zg/l, n=56, 95%CI:4.3-5.6; p=0.003). However, no effect of ethnicity on year 6 sCD23 was detectable nor did ethnicity significantly affect sCD25 levels at birth or age 6.

In a small separate population, no correlation was found between maternal and infant sCD23 (n=18, r=0.05, p=0.8). These data thus support the concept that placental transmission of sCD23 does not occur. Maternal sCD23 levels were also significantly lower than infant levels (n=18, GM=1.9 μ g/l, 95%CI:1.2-3.0 and GM=3.7 pg/l, 95%CI:3.3-4.2, respectively, p<0.05).

Year 6 sCD25 levels demonstrated a direct relation with the occurrence of skin test reactivity to common local aeroallergens (p=0.007, Fig 2). Cord sCD25 showed a similar trend (p=0.06, Fig 2).

No significant relations were found between levels of sCD23 in cord or age 6 sera and either skin

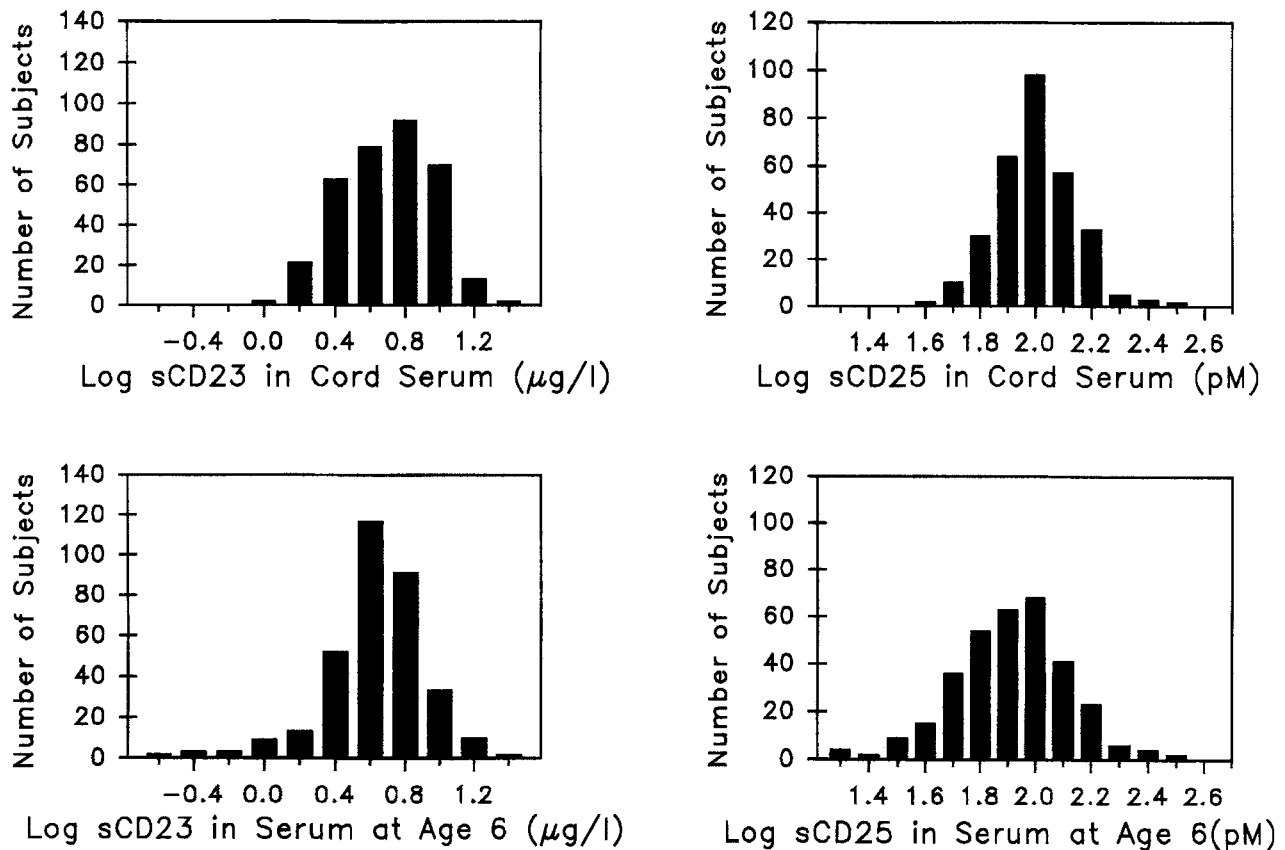


Fig. 1. Frequency distributions of log sCD23 and sCD25 at birth and age 6.

test reactivity at age 6 (Fig 2) or IgE levels in cord or age 6 sera. Despite the relation with skin test reactivity, neither cord nor age 6 sCD25 levels were significantly correlated with cord or age 6 IgE levels.

Cord and age 6 sCD23 and sCD25 values were divided into tertile groups and the prevalence of physician diagnosed active asthma, allergic rhinitis and eczema at age 6 assessed in each group. No significant association was observed between the prevalence of asthma, rhinitis or eczema at age 6 and either cord or age 6 sCD23 or sCD25 levels.

Discussion

The current study was carried out in line with our interest in delineating the *in vivo* mechanisms responsible for the development of skin test reactivity and allergic diseases and from recent studies (12–14, 19, 24, 25) suggesting that sCD23 and sCD25 might provide serum markers of the presence and/or development of allergic diseases. Because CD23 upregulation is critical to IgE class switch (10), it seemed logical that sCD23 might therefore show a significant association with either IgE level or skin test reactivity. Indeed several groups have reported such associations but they were in each case seen

only in certain age and diagnosis-specific categories (12–15) of patients. In contrast, however, in some patient groups Hoeger et al. (19) reported sCD23 levels to be lower in certain age groups of asthmatic patients compared to normals.

In regard to sCD25, Matsumoto et al. (13) reported that sCD25 levels were increased in children with atopic eczema but were not increased in children with bronchial asthma. However, Corrigan and Kay reported a relation of elevated sCD25 with asthma in adults hospitalized for exacerbations (24,25) and Hoeger et al. found that levels of sCD25 correlated with asthma severity in children <7 years old.

These studies hinting at relationships of sCD23 and sCD25 with allergic symptoms were derived from small and/or selected patient groups and thus it was important to examine these markers in a large nonselected population of children. The results of our study revealed that neither sCD23 or sCD25 levels in serum provide reliable indicators of allergic risk as no significant associations or predictive relationships were evident with current or subsequent development of asthma, allergic rhinitis or eczema. Thus, relationships that have been reported by others may only be evident with severe disease or may only apply to certain narrow age ranges.

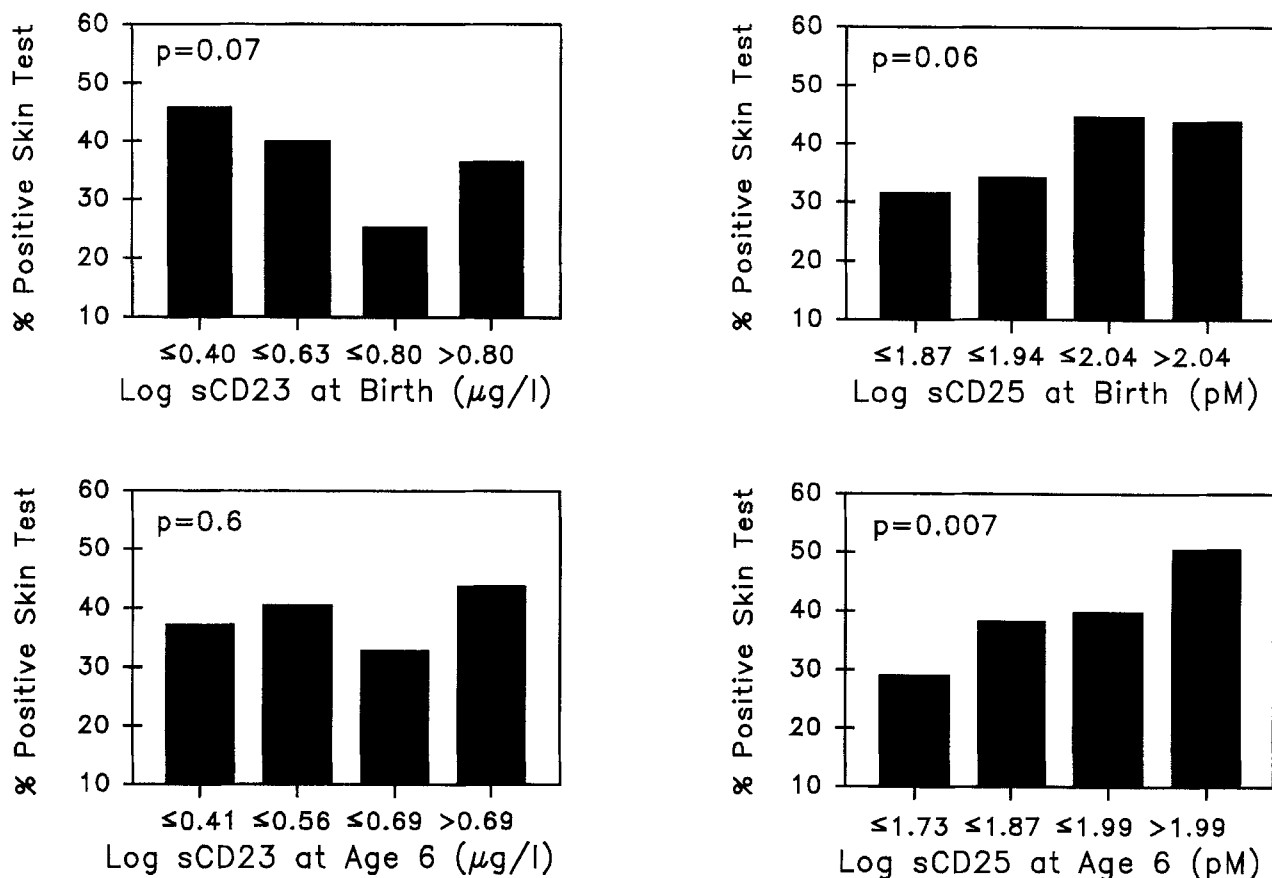


Fig. 2. Skin test reactivity at age 6 and serum levels of sCD23 and sCD25 at birth and age 6. The prevalence of children with at least one positive skin test to 7 local aeroallergens is shown for quartile groups of log sCD23 levels at birth ($n=85, 85, 83, 85$; trend chi-square $p=0.07$) and at age 6 ($n=86, 79, 85, 80$ respectively) and for log sCD25 at birth and age 6, ($n=76, 76, 76, 73$; and $n=79, 81, 83, 81$ respectively).

This lack of association of these markers with diagnoses is an important message as we try to determine correlational markers, as well as causative factors of allergic disease.

In addition to examining associations with allergic disease, we assessed possible relations of skin test reactivity with the markers. A significant association was found between age 6 skin test reactivity and sCD25 levels measured at age 6 with a similar trend seen for cord blood sCD25. Increases in sCD25 reflect upregulation of membrane CD25 on T cell surfaces during T cell activation (26) and thus these data suggest a relationship of T cell activation with the development of skin test reactivity. Although this association of sCD25 with skin test reactivity is statistically significant, a lack of specificity nevertheless makes it unlikely that this finding can provide diagnostic utility. Other inflammatory and autoimmune conditions are also associated with increased levels of sCD25 (reviewed in 22). Indeed, a recent study demonstrates an additional factor serving to dilute further any prospects for specificity, i.e., that healthy smokers also have increased serum levels of sCD25 compared with non-smokers

(27). Whether the sCD25 relationship points the way to better understanding the *in vivo* processes involved in the development of atopy remains to be determined.

It was of interest to find that (in contrast to sCD25) sCD23 levels at age 6 showed no significant association with skin test reactivity. These data should not be interpreted as indicating that sCD23 is unimportant in specific IgE synthesis *in vivo*, however, but only that any such role for this marker is not distinguishable by measuring the serum level.

Both sCD23 and sCD25 levels are higher at birth than later in childhood. Hoeger et al. also observed age related decreases in sCD23 and sCD25 from age 2 to 18 years (19). The biologic role of the high levels at birth remains to be determined.

Cord serum levels of both markers show significant associations with levels at year 6 when assessed at these two ages within the same individuals. These data suggest that at least some of the mechanisms regulating these levels are already operative at birth. The lack of correlation in levels of sCD23 between mother and newborns corroborates similar finding suggesting fetal origin for this marker (15).

Despite the correlation of sCD25 with the development of skin test reactivity, no similar relationship was demonstrable with total serum IgE levels. Levels of sCD23 also did not relate to serum IgE level. Others have previously reported similar results (13,15,19,28,29). Thus, despite the long established, close association between skin test reactivity and total serum IgE levels (30), the sCD25 findings may reflect different regulatory mechanisms operative in the initiation of IgE synthesis (as the first event in the development of skin test reactivity) compared to regulation of the maximum circulating levels (total serum IgE level).

In summary, we have demonstrated that in a large unselected population of children, serum levels of sCD23 and sCD25 are relatively high at birth, decrease by age 6, but do not show close associations with the presence or development of allergic diseases. This last finding contrasts with recent reports from small and/or selected patient populations. Our findings, however, are not surprising given recent studies indicating that these molecules are likely to be derived from many cell types, under a variety of inflammatory conditions or stimuli, and are themselves controlled by complex mechanisms (reviewed in 22, 31). Despite a lack of association with allergic disease syndromes, sCD25 levels were nevertheless associated directly with increased prevalence of immediate skin test reactivity, likely reflecting T cell activation associated with the process of allergen sensitization.

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