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Soluble CD30 serum levels in atopic dermatitis and bronchial asthma and its relationship with disease severity in pediatric age

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CD30 is a transmembrane molecule that may be expressed on a proportion of activated T-lymphocytes and has been reported to be a marker of Th2 phenotype. A soluble form of CD30 (sCD30) is released by CD30+ cells *in vivo*. Our objective was to evaluate serum sCD30 levels in children with atopic dermatitis (AD) or bronchial asthma and to investigate its relation to disease severity. This study included of 60 infants and children, of whom 18 had AD, 22 had bronchial asthma and 20 were healthy matched subjects. Severity of AD was assessed according to the objective Scoring Atopic Dermatitis (obj-SCORAD) index. Laboratory investigations included complete blood count, serum total immunoglobulin E (IgE) and serum sCD30 by ELISA. Serum levels of sCD30 in AD (77.7 ± 27.9 U/ml) and asthmatic patients (49.2 ± 21.5 U/ml) were significantly increased compared with the control group (18.2 ± 7.0 U/ml) ($t = 8.8$, $p < 0.0001$; $t = 6.4$, $p < 0.0001$, respectively). In patients with AD, sCD30 levels were shown to correlate with obj-SCORAD ($r = 0.96$, $p < 0.0001$). Patients with moderate persistent asthma had significantly elevated sCD30 levels than those with mild persistent asthma ($t = 3.4$, $p < 0.01$). In addition, sCD30 was inversely correlated to peak expiratory flow rate ($r = -0.78$, $p < 0.0001$). Levels of sCD30 did not correlate with age, disease duration or serum total IgE ($p > 0.05$). In conclusion, serum sCD30 levels correlate with the severity of AD and bronchial asthma. It appears to be an additional objective marker that may be useful for follow up and may help to improve research and management of these diseases.

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CD30 is a 120-kDa membrane-bound glycoprotein belonging to the tumor necrosis factor–nerve growth factor (TNF–NGF) receptor superfamily (1). It was originally described as a marker for Hodgkin's lymphoma cells (2–4). CD30 has been shown to be an activation marker, which is preferentially expressed on T cells with a Th2 phenotype (5–7). As Th2 lymphocytes are key cells in the pathogenesis of allergic diseases like allergic asthma and atopic dermatitis (AD) (6–8), it is intriguing to search for a differential expression of CD30 in these atopic disorders. The membrane molecule can be transformed into soluble form (sCD30) by limited proteolysis (i.e., shedding) and is released into the blood stream after cellular activation, and can then be detected in biological fluids including serum (1).

There are at least 13 scoring systems and indices for the assessment of disease severity in children with AD (9). Problems with inter- and intrapersonal variability become an unavoidable issue when using these subjective clinical indices.

Thus, it would be useful for clinicians to have an objective laboratory marker that correlates with the various clinical aspects of AD, especially the inflammatory intensity of the disease. Little is known about the effect of duration of AD and its severity, and the effect of age and gender on the soluble circulatory fragment of CD30 (sCD30). In addition, the levels of sCD30 in bronchial asthma and the effect of disease severity on it remain unclear.

With this as a background, this study was aimed to analyze serum sCD30 levels in children affected by AD or bronchial asthma and to study its relation to age, gender, disease duration and severity.

Subjects and methods

Study population

This study included 60 infants and children, of whom 18 had AD, 22 had bronchial asthma and 20 were healthy subjects enrolled as a control group. The age of the patients ranged between 6 months and 14 yr with a mean age (s.d.) of 6.2 (3.9) yr. The patients were recruited from the Pediatric Allergy and Immunology Unit and outpatient clinics of Ain Shams University Children's Hospital, Cairo, Egypt. Informed consent was obtained from the parents or caregivers of each patient or control subject before enrollment in the study.

Atopic dermatitis. The AD group comprised of 18 subjects whose ages ranged between 6 months and 8 yr with a mean age (s.d.) of 3 (2.5) yr. There were nine males and nine females. The inclusion criteria were pruritus, typical eczematous lesions, intermittent course, family history of atopy, and duration of illness longer than 6 wk (10). We excluded subjects with history of other allergic diseases, such as asthma, allergic rhinitis, or allergic conjunctivitis, in order to be able to interpret the effect of skin allergy alone. The patients were evaluated upon recruitment before the start of therapy, and children who were currently receiving systemic corticosteroids were not included. The severity of dermatitis was evaluated according to the objective Scoring Atopic Dermatitis (obj-SCORAD) index (11). In brief, obj-SCORAD defines a score for two parameters namely, extent and intensity. The extent of the lesions is calculated with the rule of nines and indicates the body surface involved. Intensity items are erythema, edema/papulation, oozing/crusts, excoriations, lichenification and dryness of non-involved skin (0–3 points for each item). The total score is calculated according to the following equation: obj-SCORAD = $(0.2 \times \text{area}) + (3.5 \times [\text{erythema} + \text{edema/papulation} + \text{oozing/crusts} + \text{excoriations} + \text{lichenification} + \text{dry skin}])$. The total obj-SCORAD score has a 0–83-point scale.

Bronchial asthma. This group included 22 children with bronchial asthma, aged 6–14 yr (mean [s.d.] = 8.8 [2.6] yr). There were 12 boys and 10 girls. The diagnosis of asthma has been based on the clinical symptoms and signs of episodic wheezing, chest tightness and dyspnea that improve at least partially after bronchodilator therapy. None of the patients suffered acute asthma exacerbation. Patients were classified following the National Heart, Lung and Blood Institute (NHLBI) guides, 2003 (12), into mild persistent asthma (n = 11) and moderate persistent asthma (n = 11). Patients with mild persistent asthma had daytime asthma symptoms more than once a week but fewer than once a day; night-time symptoms more than two times a month and peak expiratory flow rate (PEFR) ≥ 80%. Moderate persistent asthma patients were symptomatic daily, might have had night asthma symptoms more than once a week, their PEFR was 60–80% and required daily use of inhaled short-acting β_2-agonists.

The PEFR was measured by peak flow meter. As the parents did not know their children's personal best, the estimation of the expected PEFR was obtained from a standardized chart that approximates PEFR by the child's height (13). The PEFR of each patient was compared with normal population and the percent predicted PEFR was calculated.

At enrollment, 18 of the asthmatic patients were on regular corticosteroid inhalation therapy with or without long-acting inhaled β_2-agonist or sustained release theophylline. Four subjects were receiving inhaled sodium cromoglycate only as a maintenance therapy.

Control group. The controls comprised of 20 healthy infants and children. They were 11 boys and 9 girls, and their ages ranged between 6 months and 14 yr with a mean (s.d.) of 6.4 (4.3) yr. The inclusion criteria were the absence of personal or first-degree relative history of atopy or any chronic illness. They underwent general and systemic clinical examinations to exclude any current illness. We also excluded subjects who had evidence of peripheral blood eosinophilia or elevated serum total immunoglobulin E (IgE) for age.

Study measurements

Serum sCD30 assay. Serum levels of sCD30 were determined by enzyme-linked immunosorbent assay (ELISA) kit (Bender MedSystems Diagnostics GmbH, Vienna, Austria, Europe). In this procedure, serial diluted standards and diluted serum samples were added to microplate wells coated with monoclonal antibody to human sCD30. Subsequently, antibody conjugated to horseradish peroxidase was added to the wells for an incubation step. After the washing step, substrate solutions were incubated into the wells, resulting in a colored product. After the addition of phosphoric acid as a stop solution, the color was measured at 450 nm. The color intensity was proportional to the amount of sCD30 present in the sample.

Serum total IgE. Serum total IgE was assayed by ELISA (Eurogenetics, IgE Quantitative, Tessenderlo, Belgium). Results are expressed in IU/ml. Owing to the variability in serum total IgE levels with age in childhood, we calculated the percentage values from the reference ranges (14) by dividing the subject's level by the highest normal for age $\times$ 100. The IgE levels used in the correlations were both the measured and the calculated percentage values.

Complete blood count. The blood count was performed with the Coulter counter (Beckman Coulter, Inc, FL, USA). The differential leukocytic counts were also estimated manually from the blood film, and the eosinophil percentage in peripheral blood was recorded.

Statistical analysis

The results were analyzed by a commercially available computer software package (StatView; Abacus Concepts Inc, Berkeley, CA, USA). The data are presented as mean and s.d. The student's *t*-test was used to compare between two groups, as regards parametric data, and Mann–Whitney *U*-test was used for non-parametric comparisons. The correlation between the various numerical parameters was studied by the Pearson correlation coefficient (r) test. Statistical significance was defined as p value < 0.05. The receiver operating characteristic (ROC) curve analysis was used to obtain the optimal cut-off point.

Results

The characteristics of the study subjects are shown in Table 1.

Serum levels of sCD30 were significantly higher in both patients with AD (range = 33–117 U/ml, mean [s.d.] = 77.7 [27.9] U/ml) and bronchial asthma (range = 18–85 U/ml, mean [s.d.] = 49.2 [21.5] U/ml) with respect to controls (range = 8–36 U/ml, mean [s.d.] = 18.2 [7.0] U/ml) ($t = 8.81$, $p < 0.0001$; $t = 6.42$, $p < 0.0001$, respectively). Patients with AD had higher sCD30 levels than asthmatic patients ($t = 3.65$, $p < 0.001$) (Fig. 1).

The cut-off point of serum sCD30 (obtained from the ROC curve) was 28 U/ml. all the AD patients had sCD30 levels above the cut-off value, whereas 17 out of the 22 (77%) asthmatic patients had levels above the cut-off value.

Serum sCD30 levels did not correlate with age in AD, bronchial asthma or control group ($r = -0.06$, $p > 0.05$; $r = -0.04$, $p > 0.05$; $r = 0.23$, $p > 0.05$, respectively). Serum levels of sCD30 were comparable in males and females in the studied groups (in AD $t = 0.58$, $p > 0.05$; in bronchial asthma $t = 0.35$, $p > 0.05$; in controls $t = 0.95$, $p > 0.05$).

In patients with AD, obj-SCORAD ranged between 13 and 50 with a mean (s.d.) of 29.7 (11.3). A clear correlation between obj-SCORAD and sCD30 was detected ($r = 0.96$, $p < 0.0001$) (Fig. 2). Furthermore, obj-SCOR-

Table 1. Demographic features of patients with atopic dermatitis (AD), bronchial asthma and healthy controls

	AD	Bronchial asthma	Control group
Patients (n)	18	22	20
Sex (M/F)	9/9	12/10	11/9
Age (yr)	3 ± 2.5 (0.5–8)	8.8 ± 2.6 (6–14)	6.4 ± 4.3 (0.5–14)
IgE (IU/ml)	296.9 ± 226 (45–720)	469.1 ± 227 (160–960)	26.3 ± 21.2 (5–100)
Eosinophils (%)	8.8 ± 2 (5–12)	8.9 ± 2.3 (5–12)	2.7 ± 0.9 (1–4)
Obj-SCORAD*	29.7 ± 11.3 (13–50)		
PEFR† (% predicted)		78.1 ± 6.8 (65–90)	

Data are presented as mean ± s.d. with range in parentheses.
*Obj-SCORAD, objective scoring atopic dermatitis.
†PEFR, peak expiratory flow rate.

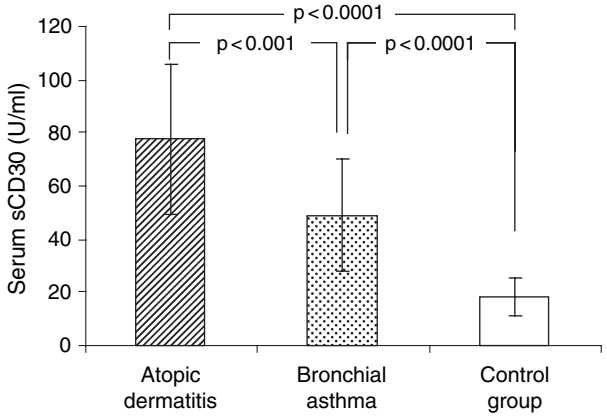

Fig. 1. Serum levels of soluble CD30 (sCD30) in the studied groups.

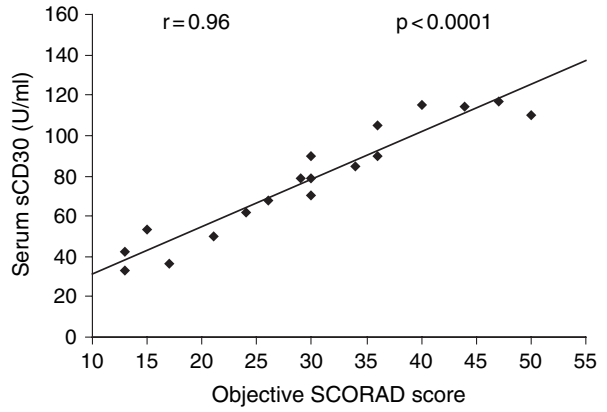

Fig. 2. Correlation between serum soluble CD30 (sCD30) levels and objective scoring atopic dermatitis (obj-SCORAD) score in AD patients.

AD demonstrated positive correlation with relative counts of eosinophils in peripheral blood ($r = 0.72$, $p < 0.001$), but was not correlated to serum total IgE concentration ($r = 0.20$, $p > 0.05$) or IgE percentages from normal ($r = -0.02$, $p > 0.05$).

Serum levels of sCD30 were significantly higher in patients with moderate persistent asthma (range = 25–85 U/ml, mean [s.d.] = 61.9 [20.9] U/ml) than patients with mild persistent asthma (range = 18–53 U/ml, mean [s.d.] = 36.6 [13.3] U/ml) ($t = 3.4$, $p < 0.01$) (Fig. 3). Serum sCD30 levels were inversely correlated to PEFR ($r = -0.78$, $p < 0.0001$) as seen in Fig. 4.

Serum total IgE levels in AD and asthmatic patients were significantly elevated compared with the control group ($z = 5.1$, $p < 0.0001$; $z = 5.5$, $p < 0.0001$, respectively). However, serum sCD30 levels did not correlate to serum total IgE concentrations or IgE percentages from normal in AD patients ($r = 0.25$, $p > 0.05$; $r =$

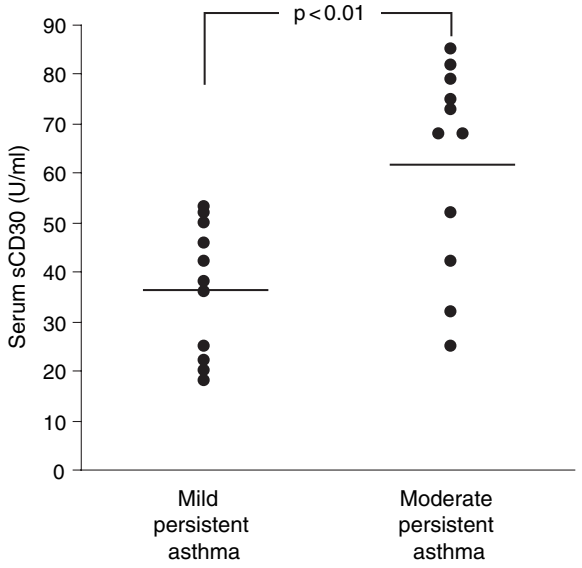

Fig. 3. Comparison of serum levels of soluble CD30 (sCD30) between patients with mild and moderate persistent asthma. Horizontal lines indicate mean values.

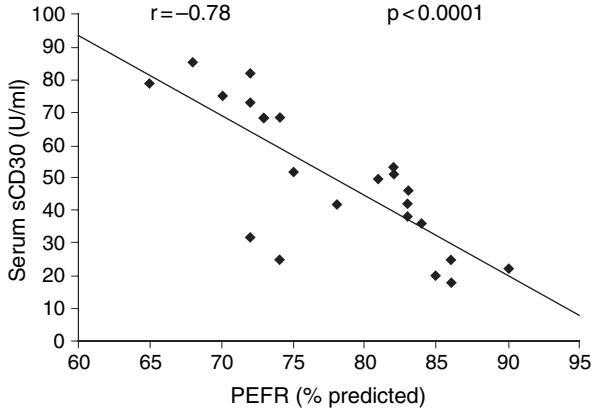

Fig. 4. Correlation between serum soluble CD30 (sCD30) levels and peak expiratory flow rate (PEFR) % predicted in asthmatic patients.

0.06, $p > 0.05$, respectively) or asthmatic patients ($r = 0.29$, $p > 0.05$; $r = 0.32$, $p > 0.05$, respectively). Positive correlations were found between sCD30 and relative counts of eosinophils in peripheral blood in both AD and asthmatic patients ($r = 0.71$, $p < 0.001$; $r = 0.81$, $p < 0.0001$, respectively). Serum sCD30 levels were not correlated to disease duration neither in AD nor in asthmatic patients ($r = -0.14$, $p > 0.05$; $r = -0.14$, $p > 0.05$, respectively).

Discussion

The results of this study revealed increased serum sCD30 levels in AD and bronchial asthma. The

high levels of sCD30 could be considered the reflection of Th2 immune response in these atopic disorders. (8, 15). An association between CD30 expression and AD has been reported (16), but none was found between it and psoriasis, seborrheic dermatitis, urticaria or contact dermatitis (17–20). Moreover, allergen exposure in atopic asthma causes significant increase in CD30 expression. A high number of CD30+ circulating cells was found in allergic patients during seasonal allergen exposure (21, 22).

CD30 exists as a membrane glycoprotein chain of 105 and 120 kDa, derived from a 90-kDa precursor and a 57-kDa intracellular form (23). The extracellular portion of CD30 is proteolytically cleaved to produce an 88-kDa soluble form of the molecule, the sCD30, which is released by CD30-expressing cells *in vitro* and *in vivo* (24, 25). CD30 expression and sCD30 release have been found to be preferentially associated with the production of Th2-type cytokines *in vitro* by both CD4+ and CD8+ human T-cell clones (5, 26).

In AD, CD30 expression on CD4+ T cells is increased in lesional skin biopsies (16, 19, 21, 27). The CD30 expression on these cells is strongly correlated with their ability to produce interleukins (IL)-4 and IL-5 and is inversely related to interferon gamma (IFN-γ) (27).

In bronchial asthma, peripheral blood CD4+ T-cell expression of CD30 correlated inversely with IFN-γ production and IFN-γ:IL-4 ratio (21). This ratio gives an idea on the balance between Th1 activity (IFN-γ) and Th2 activity (IL-4). The Th2-type cytokines, IL-4 and IL-5, have an important role in atopic disease and more specifically in atopic asthma (28, 29). IL-4 is involved in the switch of B cells to IgE production (30) and IL-5 has been shown to cause eosinophil infiltration into the airway (31).

AD is frequently associated with high IgE levels in the serum and is frequently associated with peripheral blood eosinophilia (32). In our series, we found a positive correlation between serum sCD30 and percentage of peripheral blood eosinophils. Some authors found a positive correlation between serum sCD30 levels and serum IgE levels (20), while in some studies such correlations could not be found (17, 19, 33). In our study, serum sCD30 levels were independent of serum IgE, and serum IgE did not correlate with obj-SCORAD. IgE has been shown to be a poor marker for assessing the disease strength (34, 35). Furthermore, serum IgE levels were found to be present at normal concentrations in nearly 20% of patients with AD (35, 36). However, a positive correlation between extent and severity of the disease commonly associated with respiratory atopic disease has been reported (37). Thus, IgE can be seen to be associated with a severe form of AD in general, but it does not reflect flares/exacerbations in the course of the disease, particularly through exposure to trigger factors. Consequently, it is not surprising that in patients demonstrating clinical improvement as a result of therapy, there was no transition noted in the concentration of IgE levels; these remained elevated (38).

The current study established a significant correlation between sCD30 level and disease severity of AD similar to what was previously reported by some investigators (20, 27). This positive correlation with disease severity could allow us to postulate that elevated serum levels of sCD30 are as a result of the release of membrane molecule from activated Th2 cells infiltrating skin lesions. In contrast, other investigators could not find this correlation (17, 18). Frezzolini et al. (18) assessed the severity of AD by the complete SCORAD index, which gives scores for the subjective symptoms as itching and sleep loss (0–10 points for each), in addition to the scores for extent and intensity (39). They attributed the lack of correlation with the complete SCORAD index to the relevance given by this scoring system to subjective symptoms, which are not easily evaluable in pediatric patients (11). When they graded the severity by Costa et al.'s clinical scoring systems (40), a positive correlation was found.

Previous studies concerning serum sCD30 in bronchial asthma gave inconsistent results. Some studies found increased levels (41, 42) while others did not (19). The current study revealed increased serum levels of sCD30 in bronchial asthma, which were higher in moderate than in mild persistent asthma, and they were inversely correlated to PEFR. Hence, our results indicate that the severer the asthma, the higher is the serum sCD30 level. Similarly, Leonard et al. (41) found that CD30 expression on peripheral blood CD4+ T cells was positively correlated with symptomatic disease severity score. Increased CD30 expression in severe asthmatics may reflect a greater Th2 cytokine response, causing more severe disease, and CD30 could be involved in facilitating this cytokine response or be a result of a greater Th2 response in these patients.

In summary, serum sCD30 levels were increased in pediatric patients affected by AD or bronchial asthma. It was not influenced by age or gender. In AD, serum sCD30 was correlated to obj-SCORAD. In addition, it was higher in moderate than mild persistent asthma, and it was inversely correlated to PEFR.

In conclusion, the presence of high amount of sCD30 in atopic dermatitis and bronchial asthma seems to confirm the role of this molecule as an activation marker useful for the evaluation of a Th2 immune response. The correlations observed with clinical scores and severities of these diseases indicate the role of sCD30 as an additional serologic marker for follow up and evaluation of disease activity in pediatric patients. Long-term follow-up studies may provide more data on usability of measuring serum sCD30 as a diagnostic and prognostic marker in atopic diseases.

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