

Soluble CD23 in systemic lupus erythematosus and scleroderma

Nilgün M. SAYINALP¹, İhsan ERTENLİ², İbrahim C. HAZNEDAROĞLU¹,
Sedat KIRAZ², Meral ÇALGÜNERİ², Semra DÜNDAR¹, Şerafettin KIRAZU¹

Depts. of hematology, and²Rheumatology, Hacettepe Medical School, Ankara, TURKEY

Soluble CD23 (sCD23) is a multifunctional cytokine. Detection of sCD23 in some autoimmune diseases were thought to be the indication of B-cell reactivity. The aim of this study is to determine serum level of soluble CD23 in patients with systemic lupus erythematosus (SLE) and scleroderma (Scl), and to investigate the possible role of sCD23 in the activation of autoimmune process in SLE. Eighteen patients with Scl (9 had limited cutaneous scleroderma and 9 had diffuse systemic sclerosis), 21 patients with SLE (12 in active period, 9 in inactive period at the time of the study) and 18 healthy hospital personnel as control group were included in this study. Blood samples were drawn for measurement of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), C3, C4, anti-dsDNA and sCD23 from SLE patients, for sCD23 measurement from Scl patients and control group. Serum soluble CD23 concentrations were assayed by Sandwich Enzyme Immunoassay using commercially available kits. Serum sCD23 concentrations were found high in SLE patients compared to controls (p=0.01). Also, sCD23 concentrations were found to be significantly increased in active SLE patients, compared to inactive SLE patients (p=0.004). Concentrations of CD23 were positively correlated with anti-dsDNA and negatively correlated with C3. A fair correlation was observed between sCD23 concentrations and ESR, and a weak negative correlation with C4. No correlation was found between sCD23 concentrations and concentrations of CRP. Median sCD23 concentrations of Scl patients were not statistically different from controls. For the clinical follow up of SLE patients, measurements of sCD23 together with C3, C4 and anti-dsDNA may be valuable. [Turk J Med Res 1996, 14(3): 97-101]

Keywords: CD23, Systemic lupus erythematosus, Scleroderma

Structure and functions of CD23 which is structurally identical to the low affinity receptor of IgE (FcεRII) have been widely investigated (1-4). CD23 is a 45 kD MW surface membrane glycoprotein. Membrane bound CD23 has functions in B cell activation beside being IgE receptor. It is fragmented to the soluble forms through a proteolytic process (4). Soluble CD23 (sCD23) plays a role in B and T cell differentiation (5). Detection of sCD23 was thought to be a useful indicator of the state of activation and differentiation of B-cells.

Increased B cell reactivity is a feature of several rheumatic diseases including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). sCD23 was found to be elevated in RA in both serum and synovial fluid (6-8).

Scleroderma (Scl) is a connective tissue disease characterized by collagen overproduction by fibroblasts and endothelial cell injury leading to specific clinical manifestations. Cytokines such as interleukin-1 B (IL-1 B), tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ) and IL-2 have been reported to influence fibroblast metabolism in vitro (9-12). It is known that IL-4 also induces dermal fibroblasts to secrete collagen, thus IL-4 might be involved in the pathogenesis of Scl (12). IL-4 up regulates CD23 expression on B cells and sCD23 release (13).

In this study we studied sCD23 concentrations in the sera of Scl and SLE patients and determined its

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Correspondence: Nilgün Sayinalp M.D.
Bahçelievler Son durak
Eser Sitesi B-3/10
06490 Ankara, TÜRKİYE

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correlation with acute phase reactants and anti-dsDNA in patients with SLE.

MATERIALS AND METHODS

Blood samples were obtained from 18 patients with Scl (mean age: 44±9 years, range: 25-63; F/M: 18/0), 21 patients with SLE (mean age: 32±5 years, range: 25-42; F/M:18/3) and 18 healthy hospital personnel as control group (mean age: 32±6 years, range: 24-42; F/M: 14/4) . All patients with SLE fulfilled at least 4 of the 1982 revised ARA criteria for the classification of SLE (14). The mean disease duration before start of the study was 3.2±2.1 years (range: 1-5). Among SLE patients, 12 of them were in active period with clinical symptoms and results of standard laboratory tests. Exacerbations were defined as described previously (15). Scl patients were classified according to American College of Rheumatology criteria (16). The mean duration of the disease was 7.2±4.3years (range: 3-12). Of the 18 Scl patients, 9 had limited cutaneous scleroderma and 9 had diffuse systemic sclerosis. Blood samples were drawn for measurement of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), C3, C4, anti-dsDNA and sCD23 from SLE patients; for sCD23 from Scl patients and control group. Plasma samples were stored at -20°C for study of sCD23.

Serum sCD23 concentrations were assayed by Sandwich Enzyme Immunoassay (SEIA) using commercially available kit (Bindazyme, The Binding Site, UK).

Erythrocyte sedimentation rate was measured by Westergren method. C-reactive protein, C3 and C4 was measured by nephelometry (normal range: 0-6 mg/L, 85-193 mg/dL and 12-36 mg/dL respectively). Anti-dsDNA was assayed by radio immunoassay method (Amerlegs-M, U.K., normal range: 0-7 ILT/mL).

Statistical analysis: Differences in parameters between groups were evaluated with Mann-Whitney U, and Kruskal-Wallis tests. Spearman's test was applied for detection of correlations between different study parameters.

RESULTS

Among SLE patients, 12 of them were in exacerbation period during the study. Erythrocyte sedimentation rate, C3, C4, serum anti-dsDNA and sCD23 levels of active and inactive SLE patients are shown in Table 1 (median and interquartile range-IQR). Erythrocyte sedimentation rate was significantly increased during exacerbations (median values: 24 mm/hr versus 86 mm/hr, p=0.001). Median C3 and C4 levels were 120.0 (7.5) mg/dL and 24.0 (5.5) mg/dL respectively in patients with inactive disease and decreased to 65.5 (41.3) mg/dL and 15.0 (10.0) mg/dL in active SLE patients. Median anti-dsDNA levels of active and inactive SLE patients were 4.5 (9.5) IU/mL and 80.0 (21.0) IU/mL respectively, (p=0.0001).

Soluble CD23 concentrations were found high in SLE patients compared to controls and patients with Scl (p=0.01). Distribution of the serum concentrations of sCD23 in SLE and Scl patients and control group are shown in Figure 1. In this box-plot figure, lower boundary of the box is the 25th percentile, upper boundary is the 75th percentile and the length of the box corresponds to IQR which is the difference between 75th and 25th percentiles. Lines drawn from the ends of the box, represent largest and smallest observed value that is not outlier, and horizontal line inside the box represents the median. During exacerbation period, sCD23 serum concentrations were found to be significantly increased compared to inactive SLE patients (median and IQR: 1.13 (1.2) pg/mL and 2.69 6.4) pg/mL, p=0.004).

Concentrations of sCD23 were correlated with anti-dsDNA (r = 0.67, p=0.001) and negatively correlated with C3 (r = -0.59, p=0.007) (Figure 2 and 3). A fair correlation was observed between sCD23 concentrations and ESR (r = 0.55, p=0.009), and a weak negative correlation with C4 (r = -0.51, p=0.017). No correlation was found between sCD23 concentrations and CRP.

Median sCD23 concentrations of Scl patients were 1.1 (0.1-4.5) pg/mL. This level was not statistically different from controls (median and range of sCD23

Table 1. ESR, C3, C4 and serum Anti-dsDNA and sCD23 levels of active and inactive SLE patients (Median and IQR).

	ESR (mm/hr)	C3 (mg/dl)	C4 (mg/dl)	Anti-dsDNA (IU/ml)	sCD23 (pg/ml)
Inactive SLE (n=9)	24.0(10.5)	120.0 (7.5)	24.0(5.5)	4.5(9.5)	1.13(1.2)
Active SLE (n=12)	86.0(6.3)	65.5(41.3)	15.0(10.0)	80.0(21.0)	2.69(3.4)
p value*	0.001	0.001	0.005	0.0001	0.004

active vs inactive SLE

of control group: 0.33; 0.1-2.6 pg/ml, $p=0.18$). Median sCD23 levels were also not different in patients with limited cutaneous and diffuse systemic sclerosis.

DISCUSSION

In this study we have observed elevated sCD23 levels in the sera of SLE patients. Soluble CD23 levels of patients with Scl were not different from controls. For SLE this finding agrees with the results of previous studies (8). Bansal and co-workers found that increased sCD23 levels may be important in the etiology of hypergammaglobulinemia in these patients, but could not find a direct correlation between serum sCD23 and the degree of hypergammaglobulinemia associated with SLE (8).

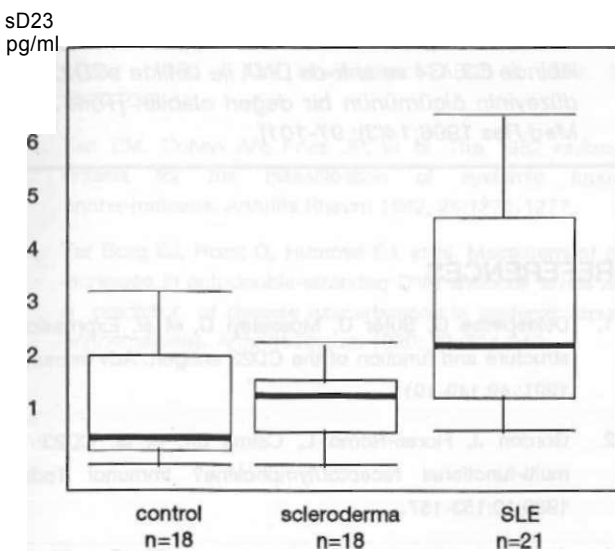


Figure 1. Boxplot graphics of the serum levels of sCD23 in SLE and Scl patients and control group. The horizontal lines inside the boxes represent medians; the upper and lower margins of the boxes correspond to 75th and 25th percentiles, respectively.

Conditions associated with B-cell proliferation appear to be together with raised level of sCD23 as noted in patients with B-CLL (17). B-cell hyperactivity has been observed in both peripheral blood and bone marrow of patients with SLE. This disease is characterized by the production of a wide range of auto antibodies. Among these, antibody to double-stranded DNA (anti-dsDNA) is considered most specific for the disease. Anti-dsDNA antibodies fluctuate with the disease activity, can be detected at high levels during active disease and thought to play important role in the pathogenesis of SLE by the formation of immune complexes that are involved in the

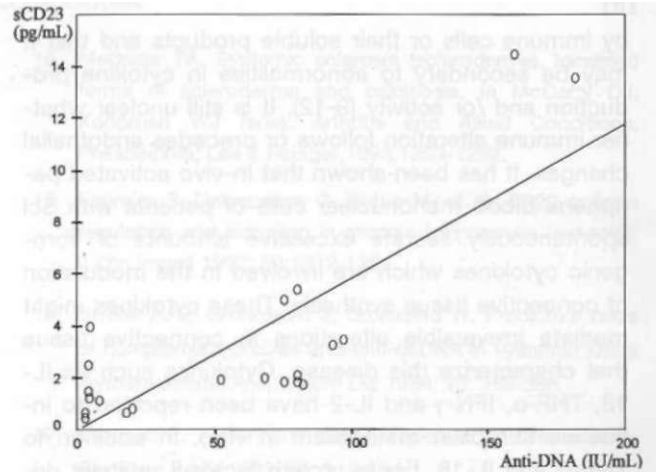


Figure 2. Correlation between sCD23 and anti-dsDNA in SLE patients (n=21)

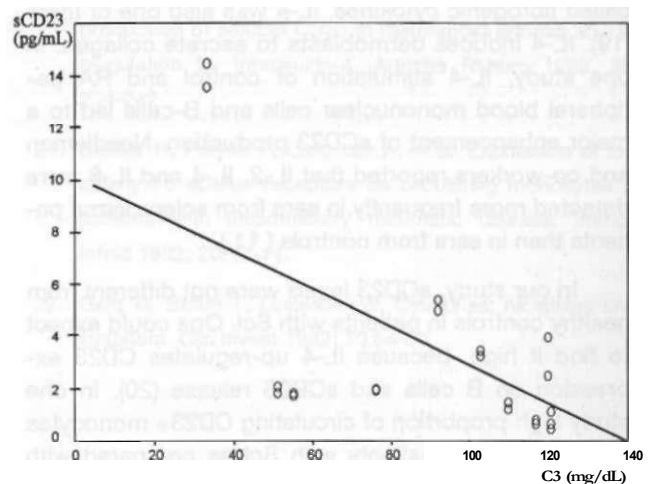


Figure 3. Correlation between sCD23 and C3 in SLE patients (n=21)

development of tissue injury (15). Also measurements of complement factors is widely used to assess disease activity. Decreased C3 as well as C4 levels have been reported to be associated with active disease in SLE. In one study serial measurements of anti-dsDNA antibodies revealed a higher sensitivity for predicting an exacerbation than did serial measurements of C3 and/or C4 (18).

In the current study, we found a positive correlation between sCD23 and anti-dsDNA antibodies, and a negative correlation between sCD23 and C3 and C4 measurements. Thus for the clinical follow up of SLE, measurements of sCD23 together with C3, C4 and anti-dsDNA may be valuable. Serial determinations of sCD23 before and during exacerbation, would give better information.

In the pathogenesis of Scl, immune activation is well established but the precise mechanism and exact trigger of immune involvement is not known (9). It is suggested that hyperactivity of fibroblasts is mediated

by immune cells or their soluble products and that it may be secondary to abnormalities in cytokine production and /or activity (9-12). It is still unclear whether immune alteration follows or precedes endothelial changes. It has been shown that in-vivo activated peripheral blood mononuclear cells of patients with Scl spontaneously secrete excessive amounts of fibrogenic cytokines which are involved in the modulation of connective tissue synthesis. These cytokines might mediate irreversible alterations in connective tissue that characterize this disease. Cytokines such as IL-1(3, TNF-a, IFN-y and IL-2 have been reported to influence fibroblast metabolism in vitro. In addition to TNF-a and IL-16, tissue growth factor-B, platelet driven growth factor and fibroblast growth factor are called fibrogenic cytokines. IL-4 was also one of them (19). IL-4 induces dermoblasts to secrete collagen. In one study, IL-4 stimulation of control and RA peripheral blood mononuclear cells and B-cells led to a major enhancement of sCD23 production. Needleman and co-workers reported that IL-2, IL-4 and IL-6 were detected more frequently in sera from scleroderma patients than in sera from controls (11).

In our study, sCD23 levels were not different from healthy controls in patients with Scl. One could expect to find it high, because IL-4 up-regulates CD23 expression on B cells and sCD23 release (20). In one study high proportion of circulating CD23+ monocytes was detected in patients with Scl as compared with controls (21). To our knowledge, there is no study in the literature about serum levels of sCD23 in patients with Scl. However, due to short half life of cytokines in the circulation or presence of serum inhibitors, serum level of a cytokine may not be found high, even when lymphocyte or macrophage activation can be demonstrated by other means (22).

Skleroderma ve sistemik lupus eritematozusta soluble CD23

Soluble CD23 (sCD23) birden fazla fonksiyonu olan bir sitokindir. Bazı otoimmün hastalıklarda tespit edilmesi B-hücre aktivitesinin belirteci olduğunu düşündürmektedir. Bu çalışmanın amacı sistemik lupus eritematozuslu (SLE) ve siklerodermalı (Scl) hastalarda serum soluble CD23 düzeyini tespit etmek ve SLE'de muhtemel otoimmün sürecin aktivasyonundaki muhtemel rolünü araştırmaktır. Bu çalışmaya 18 sklerodermalı (9 sınırlı deri hastalığı olan ve 9 difüz sistemik siklerodermalı), 21 SLE'li (12 aktif periyodlu ve 9 inaktif periyodlu) ve kontrol grubu

olarak da 18 sağlıklı hastane personeli dahil edildi. Eritrosit sedimentasyon hızı (ESR), C-reaktif protein (CRP), C3, C4, antids DNA ve sCD23 düzeylerini ölçmek için SLE'li ve Scl'li hastalardan ve kontrol grubundan sCD23 düzeyini ölçmek için kan alındı. Serum soluble CD23 düzeyi Sandviç Enzim Immunoassay ile çalışıldı. SLE'li hastalar kontrol grubuyla karşılaştırılınca, sCD23 düzeyi inaktif hasta grubuna göre anlamlı olarak yüksek bulundu (p=0.004). CD23 konsantrasyon/an anti-ds DNA ile pozitif ve C3 ile negatif korelasyon gösteriyordu. sCD23 düzeyi ile ESR ara-sında hafif bir ilişki ve C4 düzeyi ile de zayıf negatif korelasyon vardı. sCD23 konsantrasyonu ile CRP arasında ilişki bulunamamıştır. Scl'li hastaların ortalama sCD23 düzeyleri ile kontrol grubu arasında istatistiki anlamda fark bulunamadı. SLE'li hastaların takibinde C3, C4 ve anti-ds DNA ile birlikte sCD23 düzeyinin ölçümünün bir değeri olabilir. [Turk J MedRes 1996;14(3): 97-101]

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