Clinical Significance of Soluble CD31 in Patients with Systemic Sclerosis (SSc): Association with Limited Cutaneous SSc

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ABSTRACT. ***Objective.*** To determine serum levels of soluble CD31 (sCD31) and its clinical associations in patients with systemic sclerosis (SSc).

Methods. Serum sCD31 levels from 70 patients with SSc were examined by ELISA. For a longitudinal study, 64 sera from 17 SSc patients were analyzed (followup: 0.4–3.9 yrs).

Results. Serum sCD31 levels were elevated in patients with SSc (n = 70) compared with healthy controls (n = 20) and patients with systemic lupus erythematosus (n = 15). Serum sCD31 levels were higher in patients with limited cutaneous SSc (lSSc; n = 37) than those with diffuse cutaneous SSc (n = 33). Patients with elevated sCD31 levels had pulmonary fibrosis and decreased percentage vital capacity (%VC) less frequently than those with normal sCD31 levels. sCD31 levels correlated positively with %VC in patients with SSc. This association of elevated sCD31 levels with the lower frequency of pulmonary involvement and better %VC was still observed when analyzed among lSSc patients alone. The elevation of sCD31 was associated with shorter disease duration in patients with lSSc. In a longitudinal study, 75% of patients with SSc showed increased sCD31 levels only transiently in the early phase of the disease. Serum sCD31 levels remained normal during followup in all patients with normal sCD31 levels at the first visit.

Conclusion. Elevated sCD31 levels were associated with lSSc with relatively early onset and lower frequency and severity of pulmonary fibrosis. These results suggest that sCD31 would be a protective factor for the development of skin sclerosis and pulmonary fibrosis in SSc, since sCD31 has an antiinflammatory effect by inhibiting CD31 mediated transendothelial migration of leukocytes. (J Rheumatol 2001;28:2460–5)

Key Indexing Terms:
SYSTEMIC SCLEROSIS | LIMITED CUTANEOUS SYSTEMIC SCLEROSIS
SOLUBLE CD31 | PULMONARY FIBROSIS | LONGITUDINAL STUDY

Systemic sclerosis (SSc) is a connective tissue disorder characterized by fibrosis and vascular changes in the skin and other visceral organs, with autoimmune background. Although the pathogenesis of SSc remains unclear, studies suggest that some cytokines or growth factors regulate the induction of SSc by stimulating the synthesis of extracellular matrix components, injuring the endothelial cells, and modulating the function of leukocytes[1,2]. These cytokines or growth factors are produced partly by inflammatory cells infiltrating the affected tissues, such as skin or lungs, of patients with SSc[1-3].

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Migration of leukocytes into the affected tissues in patients with SSc is highly regulated by expression of various adhesion molecules[3]. The selectin family, including L-selectin, E-selectin, and P-selectin, facilitates the initial capture and rolling of leukocytes on endothelium, while intercellular adhesion molecule-1 (ICAM-1) and the vascular cell adhesion molecule-1 (VCAM-1), members of the immunoglobulin (Ig) superfamily, mediate firm adhesion of leukocytes to endothelium, followed by transendothelial migration (diapedesis)[4,5]. During transendothelial migration, the leukocytes squeeze between tightly apposed endothelial cells. This process involves the function of platelet-endothelial cell adhesion molecule (PECAM, CD31), a member of the Ig superfamily, which is expressed on the surface of monocytes, granulocytes, natural killer (NK) cells, and some T lymphocyte subsets, and is concentrated at the borders between endothelial cells[6-9]. Transmigration involves homophilic interaction of CD31 on the leukocytes with CD31 on the endothelial cells[10]. In addition, CD31 binds also to integrin αvß3, which is expressed on endothelial cells, activated T lymphocytes, mast cells, and NK cells[11].

It was reported that the soluble form of CD31 (sCD31)

was detected in human serum samples, and that sCD31 was able to inhibit CD31-specific cellular interactions[12]. Thus, sCD31 is functionally active and may potentially be involved in modulation of the inflammatory process *in vivo*. A recent study showed that circulating levels of sCD31 were elevated in patients with multiple sclerosis with active lesions, reflecting the disease activity[13].

We examined serum levels of sCD31 in patients with SSc, and related these results to clinical features. In addition, we performed a retrospective longitudinal study of sCD31 levels in some of these patients with SSc to determine changes in sCD31 levels over time.

MATERIALS AND METHODS

Serum samples. Serum samples were obtained from 70 Japanese patients with SSc (61 women, 9 men). All patients fulfilled the criteria proposed by the American College of Rheumatology (ACR)[14]. These patients were between 9 and 76 years old (mean age 45). Patients were grouped according to the classification system proposed by LeRoy, *et al*[15]: 37 patients (34 women, 3 men) had limited cutaneous SSc (lSSc) and 33 (27 women, 6 men) had diffuse cutaneous SSc (dSSc). We classified patients with skin sclerosis limited to hands, face, feet, and forearms into the lSSc category even if they had antitopoisomerase I antibodies. Inversely, patients with skin sclerosis on upper arms and trunk were classified into dSSc even if they had anticentromere antibodies. According to the criteria, 5 of 37 patients with lSSc had antitopoisomerase I antibodies while 2 of 33 patients with dSSc had anticentromere antibodies. The disease duration of patients with lSSc and dSSc was 8.3 ± 9.1 and 4.7 ± 7.2 years, respectively. Duration of disease was calculated from time of onset of the first clinical event (other than Raynaud's phenomenon) that was a clear manifestation of SSc. Five patients had been treated with low dose steroids (prednisolone, 5–20 mg/day) and 4 patients with low dose D-penicillamine (100–500 mg/day) at their first visit. No patient with SSc had received immunosuppressive therapy, or had a recent history of infection or other inflammatory diseases. Fifteen patients with systemic lupus erythematosus (SLE) who fulfilled the ACR criteria[16] were also examined as disease controls. These patients had active SLE as determined by the SLE Disease Activity Index[17]. Five patients with SLE had been treated with low dose steroids (prednisolone, 5–20 mg/day), although no patient had received immunosuppressive therapy. Twenty healthy age and sex matched Japanese persons were used as controls.

For a retrospective longitudinal study, patients whose serum samples were taken more than 3 times were analyzed. This included 64 serum samples from 17 SSc patients (16 women, one man) out of 70 SSc patients. These patients were subclassified into 9 (all women) with lSSc and 8 (7 women, one man) with dSSc. These patients were between 9 and 71 years old (mean age 51). The disease duration of patients with lSSc and dSSc at their first visit was 2.4 ± 1.5 and 1.3 ± 1.1 years, respectively. These patients had been followed for 1.9 ± 1.0 years (0.4–3.9 yrs) with 3.9 ± 0.9 (3–6) different time points. At the first visit, no patient had been treated with steroids or D-penicillamine. All 8 dSSc patients received low dose steroids (prednisolone, 5–20 mg/day) and 4 dSSc patients low dose D-penicillamine (100–300 mg/day) after their first visit. Treatment with steroids or D-penicillamine was not started in any lSSc patient, and no SSc patient received immunosuppressive therapy during the followup period. Fresh venous blood samples were centrifuged shortly after clot formation. All samples were stored at –70°C before use.

Clinical assessment. Complete medical histories, physical examinations, and laboratory tests were conducted for all patients at their first visit, with limited evaluations during followup visits. Organ system involvement was defined as described[18,19]: lung: bibasilar fibrosis on chest radiography; esophagus: hypomotility shown by barium radiography; joint: inflammatory polyarthralgias or arthritis; heart: pericarditis, congestive heart failure, or arrhythmias requiring treatment; kidney: malignant hypertension and rapidly progressive renal failure with no other explanation; and muscle: proximal muscle weakness and elevated serum creatine kinase. Pulmonary function tests, including vital capacity (VC) and diffusion capacity for carbon monoxide (DLCO), were carried out. When the DLCO and VC were < 75% and < 80%, respectively, of predicted normal values, they were considered abnormal. There were no patients with pulmonary hypertension without pulmonary fibrosis. The protocol was approved by the Kanazawa University School of Medicine and Kanazawa University Hospital, and informed consent was obtained from all patients.

ELISA. Specific ELISA kits were used for measuring serum sCD31 levels (Techne Corp., Minneapolis, MN, USA), according to the manufacturer's protocol. Each sample was tested in duplicate. The detection limit of this assay was 0.05 ng/ml.

Statistical analysis. Statistical analysis was performed by Mann-Whitney U test for comparison of sCD31 levels, Fisher's exact probability test for comparison of frequencies, and Bonferroni test for multiple comparisons. Spearman rank correlation coefficients were used to examine the relationship between 2 continuous variables. A p value < 0.05 was considered statistically significant. All data are shown as means ± SD.

RESULTS

Serum sCD31 levels in SSc. Serum sCD31 levels in patients with SSc or SLE and controls are shown in Figure 1. Serum sCD31 levels were significantly elevated in patients with

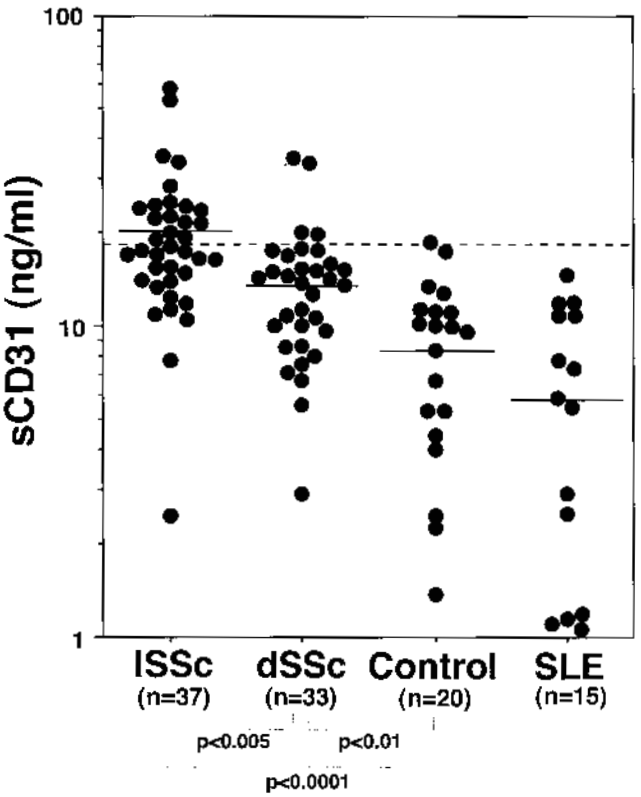

Figure 1. Serum levels of sCD31 in patients with limited cutaneous systemic sclerosis (lSSc), diffuse cutaneous SSc (dSSc), healthy controls, and SLE. Serum sCD31 levels were determined by a specific ELISA. The horizontal bar indicates the mean value in each group. Broken line indicates the cutoff value (mean + 2 SD of control samples). Note the logarithmic scale.

SSc (17.2 ± 9.7 ng/ml) compared with controls (8.8 ± 4.8 ng/ml; $p < 0.0005$) and patients with SLE (5.7 ± 5.1 ng/ml; $p < 0.0001$). There was no significant difference in sCD31 levels between patients with SLE and controls. As for subgroups of SSc, sCD31 levels in patients with lSSc (20.2 ± 10.9 ng/ml) and dSSc (13.8 ± 6.7 ng/ml) were significantly higher than in controls ($p < 0.0001$, $p < 0.01$, respectively). Further, serum sCD31 levels were significantly elevated in patients with lSSc compared with dSSc ($p < 0.005$).

Values higher than the mean + 2 SD (18.3 ng/ml) of the control serum samples were considered to be elevated in this study. Elevated sCD31 levels were observed in 30% (21/70) of SSc patients. Serum sCD31 levels were increased in nearly half of the patients with lSSc (46%, 17/37), while only 12% (4/33; $p < 0.005$) of dSSc patients had elevated sCD31 levels. Concerning clinical correlation, SSc patients with elevated sCD31 levels had digital pitting scars and contracture of phalanges less frequently than those with normal sCD31 levels (19 vs 47% and 29 vs 59%, respectively; $p < 0.05$), as shown in Table 1. Consistent with the association of elevated sCD31 levels with lSSc, SSc patients with elevated sCD31 levels had anticentromere antibodies more frequently, but had antitopoisomerase I antibodies less frequently than those with normal sCD31 levels ($p < 0.01$).

The prevalence of pulmonary fibrosis and decreased %VC in SSc patients with elevated sCD31 levels was significantly lower than in those with normal sCD31 levels (15 vs 51%, $p < 0.01$, and 16 vs 56%, $p < 0.05$, respectively). Further, sCD31 levels correlated positively with %VC in patients with SSc ($r = 0.434$, $p < 0.001$; Figure 2A). This correlation of sCD31 levels with better pulmonary function may be due to the association of elevated sCD31 levels with lSSc, since patients with lSSc have been reported to have the lower frequency of pulmonary fibrosis compared with dSSc[15]. However, sCD31 levels were also correlated positively with %VC values among lSSc patients alone ($r = 0.405$, $p < 0.05$; Figure 2B), excluding this possibility. Moreover, the prevalence of pulmonary fibrosis was significantly lower in lSSc patients with elevated sCD31 levels than those with normal sCD31 levels (1/17, 6% vs 8/20, 40%; $p < 0.05$). Although the disease duration was similar for SSc patients with elevated sCD31 levels and those with normal sCD31 levels, the disease duration in lSSc patients with elevated sCD31 levels was significantly shorter than in patients with normal sCD31 levels (4.9 ± 6.6 vs 11.4 ± 10.0 yrs; $p < 0.05$). Thus, elevated sCD31 levels were associated with lSSc with relatively early onset, with the presence of anticentromere antibodies, and with lower frequency and severity of pulmonary fibrosis.

Table 1. Clinical and laboratory data of patients with SSc showing elevated serum sCD31 levels. Values are percentages.

	Elevated sCD31, n = 21	Normal sCD31, n = 49
Age at onset, yrs, mean ± SD	47 ± 15	44 ± 17
Male:female	3:18	6:43
Duration, yrs, mean ± SD	7.5 ± 9.1	6.7 ± 8.7
Clinical features		
Pitting scars	19*	47
Contracture of phalanges	29*	59
Diffuse pigmentation	43	57
Organ involvement		
Lung	15†	51
Decreased %VC	16*	56
Decreased %DLCO	79	68
Esophagus	70	79
Heart	10	16
Kidney	0	2
Joint	10	31
Muscle	14	18
Laboratory findings		
Antitopoisomerase I antibody	10†	51
Anticentromere antibody	62†	24
Anti-U1RNP antibody	5	6
Anti-RNA polymerase antibody	5	8
Elevated ESR	43	33
Elevated CRP	14	27
Increased IgG	48	43

* $p < 0.05$ and † $p < 0.01$ vs SSc patients with normal sCD31 levels.

Longitudinal study of sCD31 levels. To assess changes in serum sCD31 levels over time, 64 serum samples from 17 patients with SSc were analyzed. The patients had relatively early onset, since the mean disease duration was 2.4 years for lSSc patients and 1.3 years for dSSc patients. At the first visit, no patient had been treated with steroids or D-penicillamine. In 5 lSSc patients with elevated sCD31 at their first visit (Figure 3A), 2 patients had stable or slightly increased levels during the followup period. In the remaining 3 patients, sCD31 levels decreased to the normal range during the followup. There was no clinical difference between lSSc patients showing stable or slightly increased sCD31 levels and those showing decreased sCD31 levels during the followup. In 4 lSSc patients with normal sCD31 levels at their first visit, sCD31 levels remained normal throughout the followup period (Figure 3B). No patient with lSSc received oral steroid or D-penicillamine, had worsening skin sclerosis, or developed new organ involvement during the observation period.

Three dSSc patients with elevated sCD31 levels at the first visit (Figure 3A) showed sCD31 levels that decreased to the normal range during followup. Since all these patients received low dose steroids immediately after their first visit, this decrease in sCD31 levels may be due to the effect of steroids. The skin sclerosis in these patients was slightly reduced, possibly in response to steroids. One patient received low dose D-penicillamine after the first visit. The elevation of sCD31 levels above the cutoff values was not detected during followup in any of the 5 dSSc patients with normal sCD31 levels at their first visit (Figure 3B). All these

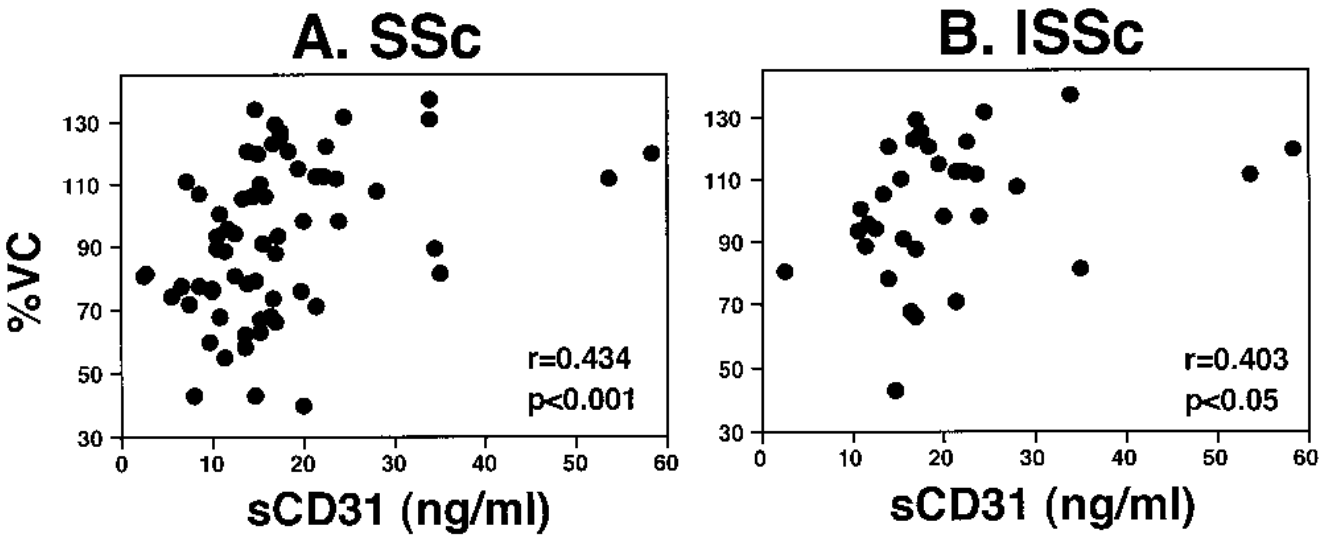

Figure 2. Correlation of percentage vital capacity against serum levels of sCD31 in patients with SSc (A) and those with lSSc (B). Serum sCD31 levels were determined by a specific ELISA.

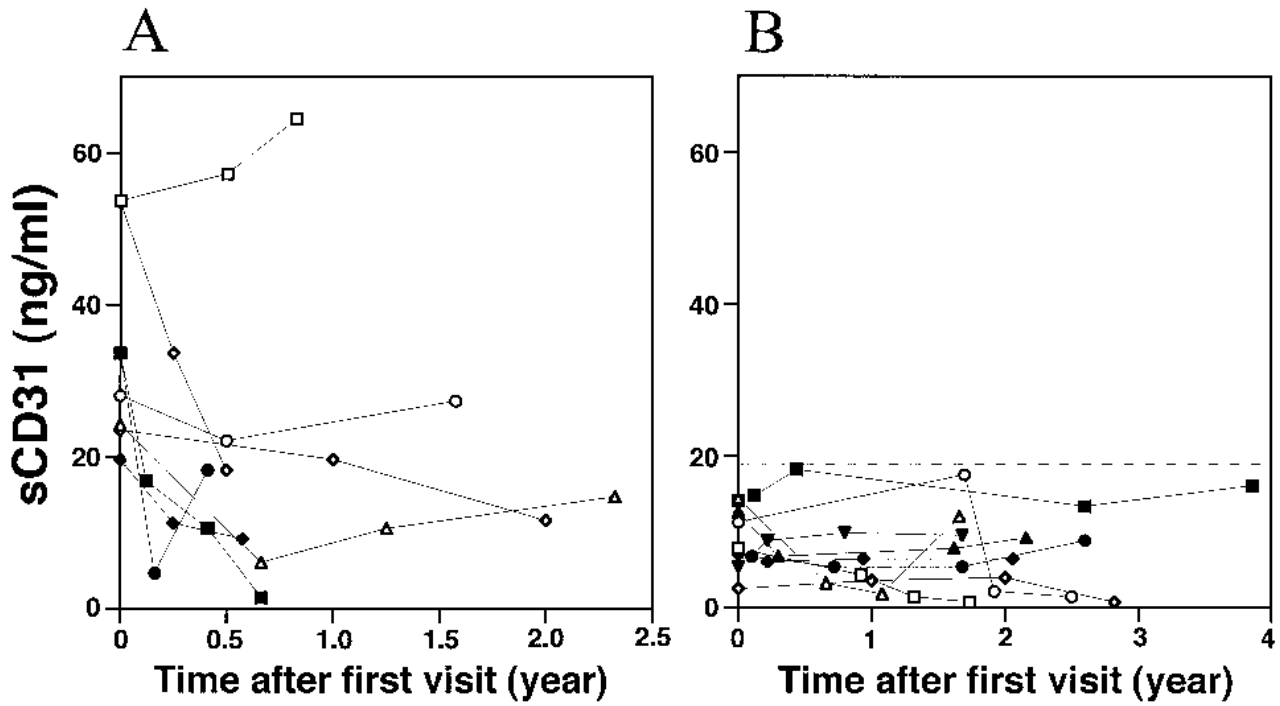

Figure 3. Serial changes of serum sCD31 levels during the followup period in SSc patients with elevated sCD30 levels at their first visit (A) and those with normal sCD31 levels at first visit (B). Serum sCD31 levels were determined by a specific ELISA. White symbols represent patients with lSSc, black symbols patients with dSSc. Broken lines indicate the cutoff value.

patients were also treated with low dose steroids after their first visit, while 3 patients received low dose D-penicillamine. Although one patient showed worsening skin sclerosis and another had subacute deterioration of interstitial pneumonitis during the followup, the remaining patients showed stable or slightly decreased skin sclerosis and did not exhibit the worsening or development of major organ involvement. Thus, the majority of patients with SSc showed increased sCD31 levels only transiently in the early phase of the disease.

DISCUSSION

Since CD31 involves transendothelial migration during interactions between cell adhesion molecules on the leukocytes and on the endothelial cells, CD31 primarily mediates a common final step in emigration for various subsets of

leukocytes[20,21]. Thus CD31 is considered an attractive target molecule for antiinflammatory or antiadhesion therapy. Indeed, it has been reported that antibodies against CD31 block acute inflammation in response to various stimuli[22-25]. Further, a soluble chimera made of the first Ig domain of CD31 fused to the Fc portion of IgG blocks transendothelial migration both *in vitro* and *in vivo*[21]. In addition, sCD31 can inhibit CD31 mediated adhesive interactions[12]. In addition to the function as a cell adhesion molecule, sCD31 is reported to inhibit T lymphocyte activation, since a soluble recombinant CD31-Ig fusion protein completely downregulated the proliferative response and cytokine production by T lymphocytes[26].

This is the first report of elevated serum sCD31 levels in connective tissue diseases. We assessed both SSc and SLE, but sCD31 levels were increased only in SSc patient sera. Interestingly, sCD31 levels were elevated in lSSc, a milder subset of SSc[15]. The elevation of sCD31 was correlated with the shorter disease duration in patients with lSSc. Further, elevated sCD31 levels were also associated with lower prevalence of pulmonary involvement and better pulmonary function in patients with SSc — this was observed even in patients with lSSc. Taken together, these results suggest that elevation of sCD31 may be a protective factor for the development of skin sclerosis and pulmonary fibrosis in SSc.

It has been reported that the soluble forms of various adhesion molecules, including L-selectin, E-selectin, ICAM-1, and VCAM-1, are elevated in sera from patients with SSc. Elevated serum levels of sE-selectin and sVCAM-1 correlate with disease severity and the presence and severity of pulmonary fibrosis in SSc[27,28]. Elevated serum sICAM-1 levels also correlate with early stages and dSSc[29,30]. Stratton, *et al* found that serum levels of sE-selectin, sVCAM-1, and sICAM-1 were elevated in SSc patients with scleroderma renal crisis[31]. Since E-selectin, ICAM-1, and VCAM-1 are expressed on endothelial cells, elevation of these cell adhesion molecules reflects the ongoing activation of endothelial cells in the disease process, leading to the development of SSc[3]. Serum levels of circulating L-selectin, which is expressed on most leukocytes, are also increased and correlate with a clinically more severe subset[32]. Thus, the soluble forms of cell adhesion molecules examined previously in SSc patients correlate with a more severe type of SSc or major organ involvement. In this study, elevation of sCD31 was strongly correlated with lSSc and lower prevalence of pulmonary involvement. To our knowledge, this is the first report showing that serum levels of a cell adhesion molecule correlated with a milder form of SSc. This suggests that sCD31 may play a specific role different from soluble forms of other adhesion molecules such as L-selectin, E-selectin, ICAM-1, and VCAM-1 in the pathogenesis of SSc, and thus CD31 would be a possible therapeutic target in this disease.

Recently, the effect of chronic administration of anti-CD31 reagents *in vivo* was addressed using transgenic mice constitutively expressing sCD31 as an IgG chimera[33]. These transgenic mice demonstrated a severely reduced acute inflammatory response, although they were otherwise healthy. These findings suggest that longterm anti-CD31 therapy would be applicable to human diseases with chronic inflammation. Our longitudinal study showed that serum sCD31 levels were elevated only transiently at the early phase of the disease process in SSc. Further, no patient exhibited elevation of sCD31 levels during the followup period after sCD31 levels decreased to normal levels or when they had normal sCD31 levels at their first visit. These results suggest that the elevated sCD31 levels and/or their duration are not enough to decrease the inflammation associated with early SSc, especially dSSc. Therefore, persistent administration of anti-CD31 reagents, including sCD31, would be a potential therapy in patients with SSc. Although dSSc patients have less active inflammation late in the disease course, sCD31 levels were not increased. It should be noted that sCD31 is not a single regulator for inflammation, and therefore the combination of various other regulators may reduce inflammation during late phase of the disease.

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