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MINIREVIEW

Clinical Use of the Measurement of Soluble Cell Adhesion Molecules in Patients with Autoimmune Rheumatic Diseases

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INTRODUCTION

Molecules that are expressed on the cell surface membrane and by binding to a specific ligand function to increase the affinity of the cell either for another cell or for components of the extracellular matrix are considered to be adhesion molecules. Based on structure, adhesion molecules fall into one of four gene families, the selectins, integrins, immunoglobulin superfamily, and cadherins (14, 18, 37). Adhesion molecules are of central importance in (auto)immune and inflammatory responses because they mediate the interactions of hematopoietic cells with endothelial cells during extravasation and homing and increase T-cell–antigen-presenting-cell contact and deliver the necessary signals for effective B-cell activation and both T-helper and T-cytotoxic cell function (18). Constitutive expression on more than one type of cells, including different subsets of lymphocytes, neutrophils, eosinophils, monocytes and macrophages, NK cells, thymocytes, platelets, dendritic cells, keratinocytes, fibroblasts, synoviocytes, muscle cells, and epithelial and endothelial cells, is characteristic of the majority of adhesion molecules (37). Cell activation, exposure to cytokines, or exposure to other soluble mediators of inflammation results in upregulation of the expression of these molecules and aberrant expression on additional cell types, whereas downregulation of their expression may occur in the presence of various pharmacological agents or blocking antibodies (14, 18, 19, 37, 44, 46). Aberrations in cell adhesive interactions in patients with autoimmune rheumatic diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc), have been reported. Overexpression of adhesion molecules at sites of inflammation and autoimmune injury in these patients has been shown at the mRNA level, as well as at the protein level, with specific monoclonal antibodies (reviewed in reference 44).

As recent experimental evidence has shown, conformational changes of adhesion molecules related to glycosylation, expression of new epitopes, and other maturation or activation processes lead to the enzymatic cleavage of cell surface molecules and the presence of soluble forms in the circulation (18, 37). Truncated adhesion molecules in which the transmembrane section is missing due to alternative mRNA splicing also circulate as soluble isoforms in vivo, even in the absence of disease (33). Culture supernatants of in vitro-activated cells contain most of the soluble adhesion molecules (16, 33). Therefore, in addition to overexpression of membrane-bound molecules, it is not surprising that increased levels of soluble forms of adhesion molecules have been found in either the serum or plasma samples of patients with autoimmune rheumatic diseases by immunoassays and bioassays. The growing interest in soluble adhesion molecules has generated production of commercially available enzyme-linked immunosorbent assay (ELISA) kits for soluble E-, L-, and P-selectins and for some of the adhesion molecules that belong to the immunoglobulin superfamily. The availability of these kits has allowed the widespread measurement of circulating adhesion molecules and their evaluation as potential laboratory tools in monitoring clinical disease activity. Numerous correlations between changes in the blood concentrations of specific molecules and parameters of disease activity or severity or response to treatment in autoimmune rheumatic diseases have been reported. This minireview focuses on the potential biological and clinical significance of selected soluble cell adhesion molecules that have been measured so far in patients with RA, SLE, vasculitis, and SSc.

SIGNIFICANCE OF SPECIFIC CIRCULATING ADHESION MOLECULE LEVEL, AS MEASURED BY ELISA, FOR HEALTH AND DISEASE

Soluble isoforms of E-selectin (endothelial leukocyte adhesion molecule-1 or CD62E), L-selectin (Mel-14 or CD62L), and P-selectin (PADGEM or CD62P), as well as adhesion molecules of the immunoglobulin superfamily, such as lymphocyte function-associated antigen-3 (LFA-3) (CD58), vascular cell adhesion molecule-1 (VCAM-1) (CD106), intercellular adhesion molecule-1 (ICAM-1) (CD54), and ICAM-3 (CD50), exist in nanogram concentrations, as determined by ELISAs, in blood samples from healthy persons (Table 1). Elevated levels of these molecules are frequently found in the blood samples of patients with infection, cancer, and inflammatory and autoimmune rheumatic diseases, including RA, SLE, vasculitis, and SSc, and probably reflect underlying cell activation. Since the expression of these molecules is broad, increased shedding does not reflect activation of any particular cell type. As a result, the use of such assays for diagnostic purposes is limited. However, these assays have provided insight into pathogenic mechanisms of disease, since elevated circulating adhesion molecule levels may have physiological in vivo effects by interfering with immune-cell–tissue-resident-cell interactions (Fig. 1) at sites of inflammation, e.g., with T-cell–endothelial-cell interactions and subsequent migration into rheumatoid synovium (16). Indeed, increased levels of soluble VCAM-1 in the synovial fluids of patients with RA may inhibit directly local T-cell activation (9). Purified soluble ICAM-1 at a concentration of 950 ng/ml can block the formation of conjugates between T-cell clones and autologous melanoma cells in vitro (3), while circulating levels of higher than 1,000 ng/ml have indeed been found in immunocompromised patients (45, 47) and pa-

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TABLE 1. Levels of selected soluble adhesion molecules in samples from healthy adult individuals, as detected by ELISAs[a]

Soluble molecule and type of sample[b]	No. of samples	Mean concn ± SD (ng/ml)[c]	Reference
E-selectin			
S	77	52 ± 18	6
S	15	35 (25–50)	34
L-selectin			
S	40	930 ± 251	40
P	18	1,600 ± 800	16
P-selectin			
S	77	220 ± 122	6
S	15	348 ± 53	21
S	40	245 ± 97	40
SF	9	11 ± 3	21
ICAM-1			
S	77	276 ± 83	6
S	15	195 (179–227)	34
S	7	191 ± 15	12
S	51	348 ± 181	39
S	82	312 ± 78	31
P		920 ± 80	28
SF	14	540 ± 35	28
VCAM-1			
S	77	574 ± 178	6
S	15	650 (585–720)	34
P, S	155	431	16
LFA-3			
S	61	18 ± 0.5	20
ICAM-3			
S	103	133 ± 91	38
SF	15	24 ± 3	21

[a] Limited to studies of patients with rheumatic diseases.
[b] S, serum; P, plasma; SF, synovial fluids from osteoarthritis patients.
[c] Parenthetical data are ranges.

tients with SLE (39) and SSc (41). The levels of recombinant E-selectin required for in vitro inhibition of leukocyte adhesion are not attained in the bloodstream; however, the possibility of this happening locally at inflammatory sites in vivo cannot be excluded (16).

The use of ELISAs for the measurement of soluble adhesion molecules in body fluids is hampered by a number of pitfalls. For a given adhesion molecule, it is possible that a significant proportion of what is shed in the circulation is missed due to adhesion to counterreceptor-bearing cells. It is also currently not known whether these kits can distinguish between inactive and active molecules, as well as whether the measurable systemic levels reflect increased synthesis or release, decreased clearance, or both (16, 33). Another major concern is the lack of internationally recognized reference preparations to act as calibrants (33). The different monoclonal antibodies used in these ELISAs should have high affinity for the measured molecule, and they should recognize all natural isoforms of the molecule (23, 33). Both the ability to detect a single isoform in a complex sample (lack of cross-reactivity) and that other substances do not modify the antigen-antibody reaction (lack of interference) are important elements for these assays. Prior to considering levels of circulating adhesion molecules as being abnormally elevated or decreased, one should always take into account the possibility that different assays report different results with the same samples because of the different monoclonal antibody specificities and standards used (23, 43). Studies that have used different antibodies for the measurement of a soluble adhesion molecule in the same sample are missing. In view of the discrepancies between the normal levels reported in several studies (Table 1), clearly due to the different ELISAs used, the development and evaluation of internationally recognized assays are warranted. Such a program, sponsored by the National Institute for Biological Standards (South Mimms, United Kingdom), is in progress (33).

Tables 2 and 3 summarize the findings of studies that have measured the levels of soluble E-, L-, and P-selectins, ICAM-1, VCAM-1, LFA-3, and ICAM-3 in blood samples from patients with rheumatic diseases by ELISAs. Some of these studies challenge each other's findings probably not only because of different control and patient groups but mainly because of the technical issues mentioned above. It is recommended that every laboratory that uses ELISAs to measure soluble adhesion molecules should establish the range of normal concentrations in samples from healthy persons that have been collected and stored under the same conditions as have the patient samples. Since normal levels may vary in different age groups or between men and women (5, 35), the use of age- and gender-matched healthy individuals as controls is necessary. In addition, a standard internal control should always be included when a new lot of a commercially available ELISA kit is run.

RA

RA is a chronic inflammatory disease that affects multiple joints. During inflammation, a massive invasion of circulating T cells, B cells, monocytes, and neutrophils in the synovium occurs. After binding to the synovial endothelium, T cells migrate into the synovial membrane and fluid. T cells interact locally with professional (auto)antigen-presenting cells, including fibroblast-like and macrophage-like cells, as well as with various proteins of the extracellular matrix. These interactions are largely mediated through adhesion molecules, a number of which are overexpressed within the joint. The endothelial expression of E-selectin is increased in an RA synovium compared to either an osteoarthritic or healthy synovium, predominantly on venules and capillaries. In contrast, L-selectin and P-selectin are not clearly upregulated in RA synovial tissues. In addition, the expression of ICAM-1 and LFA-3 is much higher in synovial fluid lymphocytes compared to that of peripheral

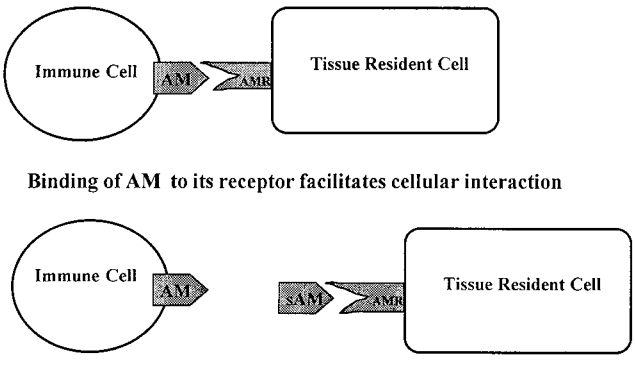

FIG. 1. Biological significance of soluble adhesion molecules. AM, adhesion molecule; AMR, adhesion molecule receptor; sAM, soluble adhesion molecule.

TABLE 2. Levels of soluble selectins, as detected by ELISAs, in the blood samples of patients with selected rheumatic diseases

Molecule and disease	Mean differences (fold)[a]	Reference(s)	Positive correlation(s)
E-selectin			
RA	1.5	36	
	1.3	6	Rheumatoid factor levels
SLE	4	9, 16	
Vasculitis	3	6	
	2	9, 16	
Kawasaki's	2	34	CRP,[b] fever, active disease
SSc	2	9 16	
	1.5	6	
	1.5	14, 17	E-selectin skin expression
L-selectin			
RA	NS[c]	40	
JRA	NS	7	
SLE	1.3	40	Serum sIL2R levels
Vasculitis	0.8	11	
Kawasaki's	0.5	16	
SSc	NS	40	
P-selectin			
RA	1.5	40	Active disease
	NS	21	
SLE	NS	40	
SSc	1.3	40	Severe disease, P-selectin skin expression, active disease (?)

[a] Significant fold difference between means for study groups of patients and healthy control individuals.
[b] CRP, C-reactive protein.
[c] NS, not significant.

RA or control lymphocytes by flow cytometry. ICAM-1 and ICAM-3 expression in situ is upregulated in RA synovial tissue vessels and lining cells compared to that of osteoarthritis and healthy subjects (reviewed in reference 44).

In general, findings regarding the levels of soluble selectins, ICAM-1, and VCAM-1 in the blood and synovial fluid samples of patients with RA are in accordance with the flow cytometry and immunohistochemical findings. Soluble E-selectin levels were increased in synovial fluids from RA patients compared to those of patients with osteoarthritis and correlated with synovial fluid leukocyte counts and soluble ICAM-1 concentrations (29). Slightly but significantly elevated levels of soluble E-selectin were found in the blood samples of patients with RA; they correlated with the presence of concomitant vasculitis (6) and fell within the first 3 days in response to treatment with anti-tumor necrosis factor alpha (TNF-α) monoclonal antibodies (36) or after treatment with sulfasalazine (49). Patients with juvenile RA (JRA) also had increased serum soluble E-selectin concentrations that correlated with the erythrocyte sedimentation rate (7). A soluble form of L-selectin was detected in synovial fluids of patients with RA, but the levels were similar to those of paired sera from these patients (22). Circulating levels of L-selectin were not significantly different between patients and healthy persons (22, 40). In contrast, the levels of soluble P-selectin were elevated in the peripheral blood of patients with RA and were significantly lower in patients who attained remission (40). Treatment with sulfasalazine also resulted in a significant lowering of serum P-selectin levels (49). The levels of soluble P-selectin in synovial fluids were increased in RA patients compared to those in osteoarthritis patients and correlated with the concentrations of soluble E-selectin and ICAM-3 (22).

The blood levels of soluble ICAM-1 in RA and JRA patients have been found to be either elevated (6, 12, 32, 36) or not significantly different compared to control levels (1, 28, 31). In these studies, soluble ICAM-1 concentrations have tended to correlate with the erythrocyte sedimentation rate, other conventional measures of RA disease activity (1, 12, 32), other circulating adhesion molecule levels (6), and an advanced stage of disease (1). A reduction in circulating ICAM-1 levels has also been observed as a result of treatment of RA patients with anti-TNF-α monoclonal antibodies (36). The levels of ICAM-1 in synovial fluids have been reported to be either higher than (32) or similar to (28) those in paired peripheral blood samples but higher than those observed in synovial fluids of patients with osteoarthritis (28, 32). Increased levels of soluble VCAM-1 in sera from RA patients that correlate with the erythrocyte sedimentation rate and C-reactive protein levels but not with soluble ICAM-1 levels have been reported (32) but not confirmed (6). Increased soluble VCAM-1 levels compared to those in paired plasma samples were also found in

TABLE 3. Levels of soluble adhesion molecules of the immunoglobulin superfamily, as detected by ELISAs, in the blood samples of patients with selected rheumatic diseases

Molecule and disease	Mean difference (fold)[a]	Reference(s)	Positive correlation(s)
ICAM-1			
RA	2.5	12	Joint score, ESR[b]
	1.5	6	Serum VCAM-1 levels, vasculitis
	2	36	
	NS[c]	1, 28, 31	
JRA	NS	7	
SLE	1.5	39	ESR, serum sIL2R levels, active disease
	NS	31	
Vasculitis	2	6	Serum VCAM-1 levels
Behcet's	1.5	2	Active disease
Kawasaki's	2	15	Active disease, serum TNF-α levels
	1.5	34	Fever, active disease
SSc	1.7	25	Serum sIL2R levels
	1.6	41	Severe disease
	1.2	6	
VCAM-1			
RA	2	16	Active disease (?)
	1.6	36	
	0.8	6	
JRA	NS	7	
SLE	4	16	Active disease (?)
Vasculitis	3	16	
	2	6	
Kawasaki's	1.2	34	Serum ICAM-1 and E-selectin levels
SSc	NS	6	
LFA-3			
RA	0.7	20	Active disease, ESR[a]
ICAM-3			
RA	NS	21	
JRA	NS	7	
SLE	1.4	38	Active disease

[a] Significant fold difference between means for study groups of patients and healthy control individuals.
[b] ESR, erythrocyte sedimentation rate.
[c] NS, not significant.

synovial fluids from patients with RA (32). Decreased levels of soluble LFA-3 in sera and synovial fluids from patients with RA, compared to normal levels and the levels of patients with other inflammatory arthritides and osteoarthritis, have been reported (20). Increased levels of soluble ICAM-3 were found in synovial fluids from patients with RA compared to those from patients with osteoarthritis and correlated with synovial fluid samples from eight RA patients; there was no correlation between the levels of soluble ICAM-3 in serum and synovial fluids (21). Interestingly, the levels of this molecule in serum do not differ between patients with RA (21) or JRA (7) and healthy individuals.

SLE AND VASCULITIS

SLE is the prototypic systemic autoimmune disease. Immunohistochemical expression of E-selectin, VCAM-1, and ICAM-1 in skeletal muscle with perivascular infiltrates, as well as in nonlesional, non-sun-exposed skin is increased in patients with SLE versus healthy controls (reviewed in reference 44). Elevated E-selectin, VCAM-1, and ICAM-1 expression in the skin is most marked during disease exacerbations (4). Increased glomerular expression of ICAM-1 was found in SLE patients and Henoch-Schoenlein purpura patients with nephritis, while de novo expression on tubular epithelial cells occurred in cases of rapidly progressive glomerulonephritis (30). The kidneys of patients with SLE nephritis or vasculitis express elevated levels of E-selectin on glomerular and tubular epithelia. In contrast, upregulation of VCAM-1 was seen only on the endothelium of interstitial vessels (8).

The levels of circulating E-selectin have been reported to be four and two times higher than normal in patients with SLE (9, 16) and vasculitis (6), respectively, including giant cell arteritis (9), polyarteritis nodosa (9, 11), and Kawasaki's disease (34). No marked differences were observed between active and inactive disease and pre- and posttreatment levels in these studies. Patients with SLE also had increased serum soluble L-selectin but not P-selectin levels that correlated with circulating soluble receptors of interleukin-2 (sIL-2R) (a T-cell activation marker), not with disease activity (40). In contrast, patients with vasculitis (11) and Kawasaki's disease (16) had levels of circulating L-selectin that were significantly lower than normal.

The mean levels of soluble ICAM-1 in serum were significantly increased in patients with SLE compared to those of healthy individuals and correlated with disease activity (27, 39). In a study of 61 patients with SLE, we found significant correlations between individual concentrations of ICAM-1 in serum and two different disease activity indices, erythrocyte sedimentation rate and levels of sIL-2R in serum, but not with levels of anti-double-stranded DNA antibodies or C4 in serum (39). These results confirmed the results of a previous study of 25 SLE patients who were found to have significantly increased levels of circulating ICAM-1 in the active state versus a less active state of the disease (27). Significant correlations between soluble ICAM-1 levels in serum and both individual disease activity and erythrocyte sedimentation rate in groups of patients with SLE were also reported by others (31). In addition to soluble ICAM-1, increased levels of VCAM-1 (16, 32) and ICAM-3 (38) in serum that appear to correlate with disease activity in patients with SLE have been reported. In a study of 16 SLE patients over an 18-month period, only VCAM-1 levels, not ICAM-1 or E-selectin levels, in serum correlated with disease activity (24); note that the monoclonal antibodies used in these ELISAs have different specificities than those used in our study (39).

Patients with systemic vasculitis, Behcet's disease, and Kawasaki's disease also had increased levels of soluble ICAM-1 (2, 11, 15, 24, 34, 50) and VCAM-1 (11, 16, 24, 34) in their sera. Blood levels of ICAM-1 correlated with clinically active disease but not with the erythrocyte sedimentation rate or C-reactive protein level in patients with Behcet's disease (2). During the acute stage of Kawasaki's disease, patients with coronary artery lesions have higher soluble ICAM-1 levels than do those without such lesions. A positive correlation with serum TNF-α levels was observed in these patients, and circulating ICAM-1 levels fell after intravenous immunoglobulin G treatment (15). Others reported that elevated levels of both soluble ICAM-1 and VCAM-1 in patients with vasculitis fell but did not normalize during periods of inactive disease, probably suggesting that treatment of these patients suppresses only the clinical manifestations, not the underlying pathogenic process (24).

SSc

SSc is a progressive condition characterized by inflammation and fibrosis of the skin and internal organs. Autoimmune mechanisms that operate in patients with SSc, as well as the presence of activated fibroblasts, smooth muscle cells, endothelial cells, and lymphocytes, including T cells, have been documented (10, 42). Several studies have suggested that overexpression of selected adhesion molecules contributes to the homing and local perpetuation of activation of pathogenic lymphocytes to the skin of patients with early scleroderma (reviewed in reference 44). Endothelial cells that express E-selectin are found in early-scleroderma skin but not in normal skin. Overexpression of E-selectin at the mRNA and protein levels was also observed in salivary endothelial cells of patients with SSc (19). P-selectin overexpression was commonly found on endothelial cells in skin biopsies taken from patients with early scleroderma (10, 17, 44), and scleroderma-derived fibroblasts expressed significantly higher levels of surface ICAM-1 than did normal fibroblasts (46).

The levels of circulating E-selectin in patients with SSc have been reported to be significantly higher than normal (6, 9). No significant differences were observed between active and inactive disease in these studies (9); however, others reported that elevated soluble E-selectin levels in serum correlated with in situ expression in scleroderma skin (17). In a study that examined serial sera from 12 patients, a decrease in circulating E-selectin, as well as circulating VCAM-1, was associated with an improvement of renal function and softening of the skin in the majority of patients (13). Increased P-selectin levels in serum were also found in patients with SSc, with the levels in patients with early-onset disease being significantly higher (40), and correlated with in situ skin expression, suggesting that in this case, elevated soluble levels did not reflect decreased clearance but rather increased production (17). On the other hand, normal circulating levels of L-selectin were found in these patients (40).

Increased levels of soluble ICAM-1 (6, 17, 25, 41, 48) in serum have been found in patients with SSc. Patients with early rapidly progressive disease had the highest levels, which correlated with the expression of membrane-bound ICAM-1 on skin endothelial cells and fibroblasts (17, 41). Increased serum ICAM-1 levels were not associated with the extent of skin or internal-organ involvement but correlated significantly with levels of sIL-2R in serum (25, 41). Patients with vasculitic digital ulcers had significantly elevated serum ICAM-1 concentrations, not sIL-2R levels (41). Increased levels of soluble ICAM-1 and sIL-2R can also be detected in suction blister

fluids from both involved and uninvolved scleroderma skin compared to those of healthy volunteers (48). Increased circulating levels of VCAM-1 (13, 17) that correlate with VCAM-1 skin expression have also been reported but not confirmed (6).

CONCLUSIONS

Soluble isoforms of E-selectin, L-selectin, and P-selectin, as well as some adhesion molecules of the immunoglobulin superfamily, such ICAM-1, VCAM-1, LFA-3, and ICAM-3, have been identified in nanogram concentrations in blood samples from healthy persons. Elevated levels of these molecules, as determined by ELISAs, have been found in many disease states, including RA, SLE, vasculitis, and SSc, probably but not necessarily reflecting underlying cell activation. Circulating adhesion molecules may influence pathogenetic mechanisms in these patients by interfering with cell-cell interactions. Specific adhesion molecule (over)expression confined to any particular autoimmune rheumatic disease has not yet been described; therefore, such assays are of limited diagnostic value. The availability of commercial ELISAs has facilitated the performance of studies that have attempted to establish clinical correlations between levels of circulating adhesion molecules and rheumatic disease activity or severity or specific disease manifestations. The various antibody specificities and standards used in these assays account for some discrepancies between related findings in different studies. Until the development of internationally recognized assays for the measurement of these molecules, physicians should consider the possibility that different assays report different results with the same samples. Additional cross-sectional studies of small groups of patients are of limited importance. At present, the clinical value of specific soluble adhesion molecules is hampered by the absence of large prospective controlled studies. Such studies are needed prior to evaluation of the quantitation of circulating adhesion molecules, alone or in combination, in monitoring and assessing the response to treatment or prognosis in patients with autoimmune rheumatic diseases.

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