

Serum thrombomodulin in systemic lupus erythematosus and juvenile idiopathic arthritis

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Thrombomodulin is a thrombin receptor on the vascular endothelial cell surface which is likely released upon endothelial cell damage. Serum soluble thrombomodulin (sTM) was assessed and investigated as a parameter of disease activity in children and adolescents with systemic lupus erythematosus (SLE) and juvenile idiopathic arthritis (JIA). Patients included in this study were regularly attending the Allergy and Immunology Clinic, Children's Hospital, Ain Shams University. They were 38 (76%) females and 12 (24%) males, their ages ranged between 5 and 18 years with a mean of 14.3 ± 4.84 years and median of 13 years. They were divided into two groups: SLE group which included 20 patients and JIA group which included 30 patients; and the control group which included 30 healthy age and sex-matched individuals for comparison. Disease activity in SLE patients was evaluated by systemic lupus erythematosus disease activity index (SLEDAI) score, while in JIA patients disease activity was determined by number of joints with active arthritis, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Serum levels of sTM were determined by enzyme-linked immunosorbent (ELISA) assay. Serum levels of sTM were significantly higher in SLE and JIA patients in comparison with the control group; there was no significant difference between SLE and JIA patients. In SLE patients, a highly significant correlation was found between sTM and SLEDAI score ($r = 0.99$, $p < 0.001$). In JIA patients, a highly significant correlation was found between sTM and number of joints with active arthritis as well as ESR ($r = 0.85$, $p < 0.001$; $r = 0.93$, $p < 0.001$, respectively). Levels of sTM were significantly higher in CRP-positive than CRP-negative JIA patients. Serum sTM is a useful serologic marker of disease activity in SLE and JIA. It may prove to be a potential indicator for early and more aggressive treatment. Furthermore, sTM may prove to be an important marker for vasculitis in general.

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Thrombomodulin (TM) is a thrombin receptor on the vascular endothelial cell surface. It inhibits the procoagulant activities of thrombin and is a cofactor for the thrombin-catalyzed activation of protein C. Activated protein C (APC) inactivates coagulation factors Va and VIIIa, thereby retarding the reaction processes of the coagulation cascade. Thus TM plays a major role in the

regulation of intravascular coagulation and is considered as a natural anticoagulant (1, 2). In addition to the membrane bound TM, a soluble form of TM (sTM) is found in the serum, plasma, and urine. As demonstrated *in vitro*, sTM is most likely released upon endothelial cell damage (3). So sTM might be a marker for endothelial cell lesions as a result of vasculitis (4, 5).

Systemic lupus erythematosus (SLE) is an autoimmune disease with multiple organ involvement. Since organ involvement in SLE is due to a vascular inflammatory process, a marker of endothelial cell damage may indicate active vasculitis in SLE (5).

Juvenile idiopathic arthritis (JIA) (6), previously termed juvenile chronic arthritis (JCA) in Europe (7), and juvenile rheumatoid arthritis in North America (8) is a chronic, systemic disorder characterized by articular joint inflammation and destruction. Several lines of evidence indicate that the hemostatic mechanism is closely linked to the inflammatory process in RA. It has been found that in RA-associated synovial effusions, biologically active TM is increased the source of which may be from plasma, neutrophils and/or synovial lining cells. TM may play a regulatory role either in fibrin deposition in the inflamed joint and/or in the progression of the inflammatory process (9).

The aim of this study was to (i) measure the serum levels of sTM in patients with SLE and JIA, (ii) compare it with healthy controls, and (iii) correlate the level of TM with clinical and laboratory parameters of disease activity.

Subjects and methods

Patients and controls

This study included 50 children and adolescents [38 (76%) females, 12 (24%) males, 5–18 years old with median = 13 years and mean $\pm$ SD = 14.3 ± 4.84 years] with SLE and JIA. Thirty healthy children [19 (63%) females, 11 (37%) males, 5–18 years old with median = 10 years and mean $\pm$ SD = 10.9 ± 4.68 years] were included as control group.

All patients were seen in the Pediatric Allergy and Immunology Clinic, Ain Shams University Children's Hospital. Patients were divided into two groups; SLE and JIA group.

The SLE group included 20 patients with SLE fulfilling the 1982 American Rheumatism Association Revised Criteria for diagnosis of SLE at the time of diagnosis (10). This group comprised one male (5%) and 19 females (95%) (age 6–18 years; median 14.5 years; mean 14.20 ± 3.24 years; and mean disease duration 4.20 ± 3.04 years). All SLE patients were receiving oral corticosteroids in a dose ranging from 0.5 to 2 mg/kg/day with a maximum dose of 60 mg/day. Three patients (15%) were receiving non-steroidal anti-inflammatory drugs (NSAIDs) in the form of ibuprofen. Four patients were receiving pulsed intravenous cyclophosphamide

in a standard protocol of 600 mg/m² monthly for 7 months, followed by every 3 months for an additional 30 months (the number of doses received by the patients ranged from seven to 12 doses).

The JIA group included 30 patients with JIA, fulfilling the international League of Associations for Rheumatology (ILAR) criteria for the diagnosis of JIA (6). They were 11 males (37%) and 19 females (63%). Their ages ranged from 5–16 years with a median of 12 years and a mean of 11.6 ± 3.31 years and a mean disease duration of 4.40 ± 3.65 years. JIA patients were classified according to ILAR Classification criteria for JIA (6). Seventeen patients had polyarthritis, six patients had systemic arthritis and seven patients had oligoarthritis. All JIA patients were receiving NSAIDs in the form of ibuprofen in a dose ranging from 10 to 30 mg/kg/day. Twelve patients (40%) were on oral steroids in a dose ranging from 0.25 to 1.5 mg/kg/day, six patients (20%) were on oral methotrexate in a dose of 10 mg/m² surface area/week and five patients (16.6%) were receiving both oral steroids and oral methotrexate.

Concerning SLE patients; 11 had both central nervous system (CNS) and renal manifestations, four had renal without CNS manifestations, one had CNS without renal manifestations and four had neither CNS nor renal manifestations. CNS manifestations were in the form of cognitive dysfunction, severe anxiety, seizures or neurologic signs (unilateral or bilateral distal weakness with signs of pyramidal lesion, besides lower motor cranial nerve lesion localized to the brain stem or sensory changes suggesting of peripheral polyneuropathy). Renal biopsy was undertaken to patients having manifestations of renal disease (n = 15). Ten patients (67%) had WHO class IV nephritis (diffuse proliferative lupus nephritis), three patients (20%) had WHO class III nephritis (focal segmental lupus nephritis) and two patients (13%) had class II-B nephritis.

Disease activity was determined in SLE patients by systemic lupus erythematosus disease activity index (SLEDAI) score. This index takes into consideration 24 variables representing nine organ systems. Each variable is rated as (present or absent) over 10 days before, and including the day of evaluation. The maximum theoretical score is 105, but in practice few patients have scores greater than 45 (11). In JIA patients, the disease activity was evaluated by the number of joints with active arthritis, CRP, and ESR (12). Active arthritis was defined as: presence of swelling or, if no swelling is present, limitation

of motion accompanied by heat, pain, or tenderness(12, 13).

Since serum sTM is frequently increased in chronic renal failure (14), the SLE patients with serum creatinine levels more than 20 mg/l were excluded from the study. Patients with evidence of infection were excluded as well.

Collection of blood samples

For sTM assay 2.5 ml of venous blood were withdrawn from each subject, left to clot at room temperature for 30 min and then centrifuged at 1500 *g* for 15 min. Serum was separated into sterile aliquots and was stored at -70°C till the time of assay of sTM.

Assays

Hemoglobin, white blood cell and platelet count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urine analysis, urinary proteins, serum creatinine, levels of serum complement component C3, antinuclear antibody (ANA) and anti-DNA were determined using standard tests.

Serum sTM was measured using Imubind Thrombomodulin ELISA kit (American Diagnostica Inc., Greenwich, CT, USA). The Imubind thrombomodulin ELISA is a 'sandwich' ELISA employing a monoclonal antibody which recognizes the epidermal growth factor-like domains of TM (EGF1-EGF2). Specificity of the capture antibody for native, complexed and truncated TM was confirmed by Western blot analysis. Samples were incubated in microtest wells pre-coated with the capture antibody. A second horseradish peroxidase (HRP)-conjugated monoclonal antibody specific for the EGF5-EGF6 domains recognizes the bound TM, completing the antibody-antigen-antibody 'sandwich'. The addition of perborate/3, 3', 5, 5'-tetramethylbenzidine (TMB) substrate and its subsequent reaction with the HRP creates a blue-colored solution. Sensitivity is enhanced by addition of a sulfuric acid stop solution, turning the solution color yellow. TM levels were determined by measuring solution absorbances at 450 nm and comparing the values with these of a standard curve.

Statistical analysis

The data were expressed as mean $\pm$ SD. Data was compared by Student's *t*-test and Mann-Whitney Z-test. Correlation coefficients were determined by linear regression analysis. Significance defined at $p < 0.05$ levels.

Results

The mean $\pm$ SD of sTM levels in SLE, JIA and control groups were 17.26 ± 11.33 ng/ml (range 3.4–31.8), 18.52 ± 11.7 ng/ml (range 3.6–32.4) and 3.85 ± 0.81 ng/ml (range 1.5–5.3), respectively. As shown in Fig. 1, sTM was significantly higher in SLE and JIA patients than controls ($z = 3.26$, $p < 0.01$; $z = 5.1$, $p < 0.001$, respectively). There was no significant difference between SLE and JIA patients ($z = 0.88$, $p > 0.05$).

Table 1 shows that in SLE patients no significant correlation was found between sTM and age ($r = -0.02$, $p > 0.05$) or duration of illness ($r = 0.11$, $p > 0.05$). Serum sTM was negatively correlated to WBCs count but this negative correlation did not reach statistical significance ($r = -0.31$, $p > 0.05$). Highly significant positive correlation was found between sTM level and SLE disease activity index (SLEDAI) score ($r = 0.99$, $p < 0.001$) as shown in Fig. 2 as well as between sTM level and ESR ($r = 0.96$, $p < 0.001$).

Significantly negative correlation was found between sTM level and hemoglobin (Hb) level ($r = -0.46$, $p < 0.05$), as well as between sTM level and platelet count ($r = -0.61$, $p < 0.01$) also between sTM level and complement C₃ level ($r = -0.86$, $p < 0.001$).

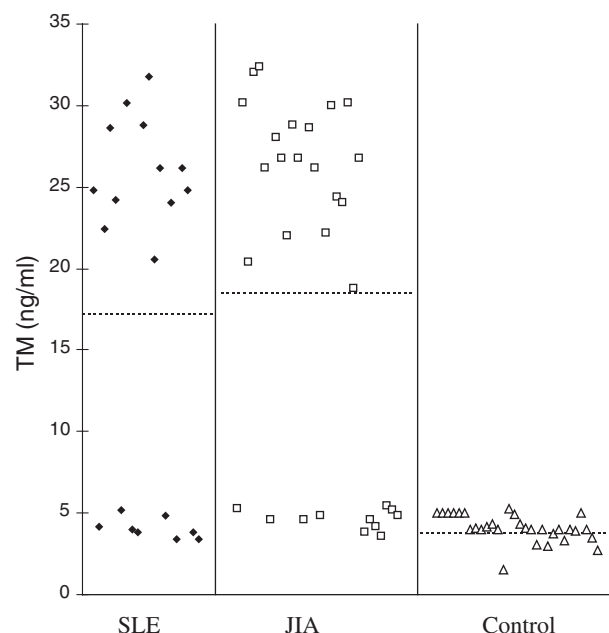


Fig. 1. Serum level of serum soluble thrombomodulin (sTM) in systemic lupus erythematosus (SLE) patients ($n = 20$), juvenile idiopathic arthritis (JIA) patients ($n = 30$), and controls ($n = 30$). The line shows the mean value in each group.

Table 1. Correlation between serum soluble thrombomodulin (sTM) and clinical and laboratory data in patients with systemic lupus erythematosus (SLE)

Variable	Range of variable	Mean $\pm$ SD of variable	Correlation with sTM	
			r	p
Age (years)	6–18	14.20 $\pm$ 3.24	–0.02	>0.05 (NS)
Duration of illness (years)	1–10	4.20 $\pm$ 3.04	0.11	>0.05 (NS)
WBC count (cell $\times 10^3/\text{mm}^3$)	2–12.5	6.40 $\pm$ 3.27	–0.31	>0.05 (NS)
Hb (g/dl)	5.9–14	9.73 $\pm$ 1.91	–0.46	<0.05 (Sig.)*
Plt. count ($\times 10^3/\text{mm}^3$)	50–786	264.40 $\pm$ 160.35	–0.61	<0.01 (HS)*
ESR (mm/h)	5–100	56.75 $\pm$ 34.04	0.96	<0.001 (HS)*
C ₃ (mg/dl)	20–132	55.00 $\pm$ 33.27	–0.86	<0.001 (HS)*
SLEDAI score	5–57	33.35 $\pm$ 19.94	0.99	<0.001 (HS)*

NS, non-significant; HS, highly significant; Sig., significant; Plt., platelet; WBC, white blood cell; Hb, hemoglobin; ESR, erythrocyte sedimentation rate; C₃, serum complement component; SLEDAI, systemic lupus erythematosus disease activity index.

Serum sTM was higher in anti-DNA positive than anti-DNA negative SLE patients [$n = 12, 8$, respectively; mean $\pm$ SD of sTM = 26.05 ± 3.28 and 4.08 ± 0.64 , respectively; $z = 3.70$, $p < 0.01$).

In SLE patients sTM was found to be significantly higher in patients with both CNS and renal manifestations ($n = 11$, mean $\pm$ SD of sTM = 26.22 ± 3.88 ng/ml) than those with either CNS or renal manifestations ($n = 5$,

mean $\pm$ SD of sTM = 8.36 ± 8.88 ng/ml) and those with neither CNS nor renal manifestations ($n = 4$, mean $\pm$ SD of sTM = 3.75 ± 0.41 ng/ml) [$z = 2.78$, $p < 0.01$; $z = 2.87$, $p < 0.01$, respectively]. There was no statistically significant difference between patients with either CNS or renal manifestations and those with neither CNS nor renal manifestations ($z = 1.47$, $p > 0.05$).

In JIA patients highest level of sTM was in systemic arthritis (29.13 ± 2.18 ng/ml), which was significantly higher than both polyarthritis (17.06 ± 11.18 ng/ml) and oligoarthritis (12.99 ± 10.57 ng/ml). There was no significant difference between polyarthritis and oligoarthritis (Fig. 3).

In JIA, sTM was significantly higher in CRP-positive JIA patients ($n = 7$, mean $\pm$ SD of sTM = 28.23 ± 3.89 ng/ml) than CRP-negative patients ($n = 23$, mean $\pm$ SD of sTM = 15.57 ± 11.02 ng/ml, $z = 2.79$, $p < 0.01$).

As shown in Table 2, in JIA patients, no significant correlation was found between sTM and age ($r = -0.05$, $p > 0.05$), or duration of illness ($r = -0.21$, $p > 0.05$), or WBCs count ($r = -0.16$, $p > 0.05$), or Hb% ($r = -0.25$, $p > 0.05$), or platelet count ($r = 0.15$, $p > 0.05$). Highly significant positive correlation was found between sTM and ESR ($r = 0.93$, $p < 0.001$), as well as between sTM and number of joints with active arthritis [$r = 0.85$, $p < 0.001$ (HS)].

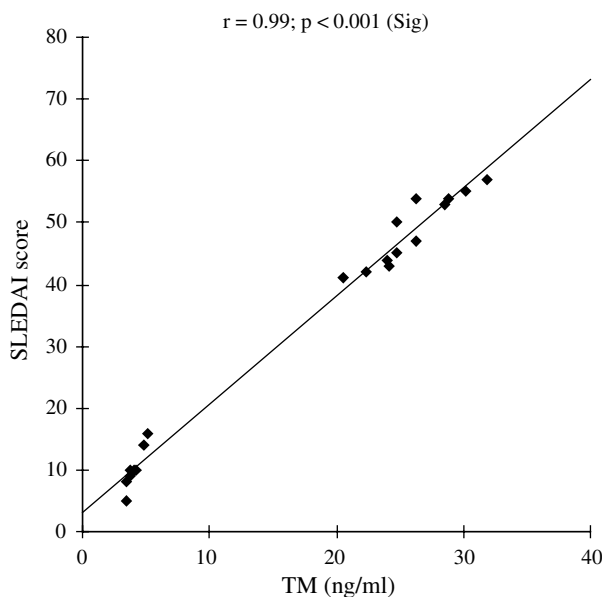


Fig. 2. Correlation between serum soluble thrombomodulin (sTM) and systemic lupus erythematosus disease activity index (SLEDAI) score in systemic lupus erythematosus (SLE) patients.

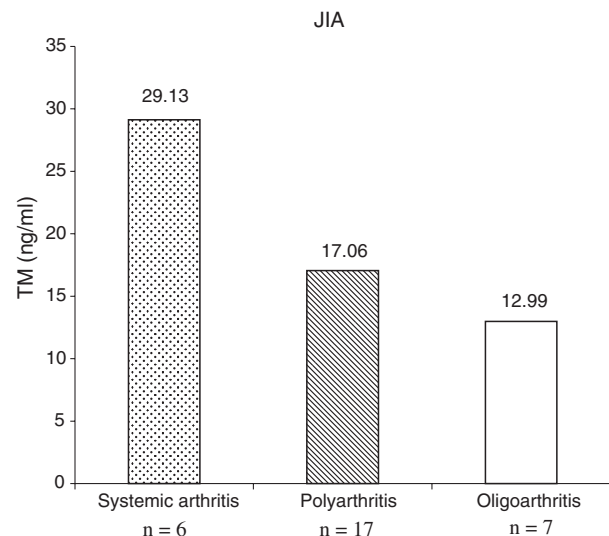


Fig. 3. Serum soluble thrombomodulin (sTM) level among the three subgroups of juvenile idiopathic arthritis (JIA). Oligoarthritis vs. polyarthritis: $z = 0.92$, $p > 0.05$ (NS). Oligoarthritis vs. systemic arthritis: $z = 3.00$, $p < 0.01$ (HS).* Polyarthritis vs. systemic arthritis: $z = 2.49$, $p < 0.05$ (Sig.).*

Table 2. Correlation between serum soluble thrombomodulin (sTM) and clinical and laboratory data in patients with juvenile idiopathic arthritis (JIA)

Variable	Range of variable	Mean $\pm$ SD of variable	Correlation with sTM	
			r	p
Age (years)	5–16	11.60 $\pm$ 3.31	–0.05	>0.05 (NS)
Duration of illness (years)	1–12	4.40 $\pm$ 3.65	–0.21	>0.05 (NS)
No. of joints with active arthritis	0–4	1.43 $\pm$ 1.36	0.85	<0.001(HS)*
WBC count (cell $\times 10^3/\text{mm}^3$)	2–33	10.42 $\pm$ 5.59	–0.16	>0.05 (NS)
Hb (g/dl)	6.5–12.9	9.95 $\pm$ 1.73	–0.25	>0.05 (NS)
Plt. count ($\times 10^3/\text{mm}^3$)	191–883	397.63 $\pm$ 181.18	0.15	>0.05 (NS)
ESR (mm/h)	5–85	40.33 $\pm$ 25.19	0.93	<0.001(HS)*

Plt., platelet; WBC, white blood cell; Hb, hemoglobin; ESR, erythrocyte sedimentation rate.

Subgroups of JIA were analyzed separately. In both oligoarthritis and polyarthritis group, there was still a significant positive correlation between sTM and ESR ($r = 0.96$, $p < 0.05$; $r = 0.94$, $p < 0.05$, respectively), and a significant positive correlation between sTM and number of joints with active arthritis ($r = 0.77$, $p < 0.05$; $r = 0.8$, $p < 0.05$, respectively).

Concerning the effect of treatment on sTM in SLE patients; there was no significant difference between the patients receiving cyclophosphamide and those not receiving it. In JIA, sTM was significantly lower in patients receiving steroids than patients not receiving them, whereas there was no significant difference in sTM levels between those receiving and those not receiving methotrexate (Table 3).

Table 3. Effect of treatment on serum soluble thrombomodulin (sTM) levels

	n	Range (ng/ml)	Mean $\pm$ SD (ng/ml)	z	p
SLE patient receiving cyclophosphamide	4	4–28.8	20.4 $\pm$ 11.13	0.52	>0.05 (NS)
SLE patient not receiving cyclophosphamide	16	3.4–31.8	16.48 $\pm$ 11.6		
JIA patients receiving steroids	17	3.6–30	15.79 $\pm$ 11.15	1.99	<0.05 (Sig.)
JIA patients not receiving steroids	13	4.6–32.4	22.1 $\pm$ 10.5		
JIA patients receiving methotrexate	11	3.8–32	18.44 $\pm$ 11.66	0.15	>0.05 (NS)
JIA patients not receiving methotrexate	19	3.6–32.4	18.57 $\pm$ 11.21		

SLE, systemic lupus erythematosus; JIA, juvenile idiopathic arthritis.

Discussion

Systemic lupus erythematosus is an autoimmune disease of unknown etiology, which is characterized by the production of a variety of autoantibodies, B-cell hyperactivity, T-cell abnormalities and multiple organ involvement (15, 16). As organ involvement in SLE is due to a vascular inflammatory process, serum sTM which is a proposed marker of endothelial cell damage may indicate active vasculitis in SLE (17).

The process of inflammation in rheumatoid arthritis (RA) is likely driven by a variety of interactions between cells, cell surface receptors, growth factors, cytokines, and lymphokines (16). However, several lines of evidence indicate that the hemostatic mechanism is closely linked to the inflammatory process. TM, a natural anticoagulant, is synthesized by various cells which are recognized in the inflammatory lesions of RA may play a regulatory role either in fibrin deposition in the inflamed joint and/or in the progression of the inflammatory process (9).

So, this study was aimed to measure the serum levels of sTM in patients with SLE and JIA and to compare it with healthy controls, and to correlate the level of sTM with clinical and laboratory parameters of disease activity in SLE and JIA to see if it could be a good serologic marker of disease activity.

Results of this study showed that serum sTM levels were higher in SLE patients in comparison with control levels. Similar results have been reported by previous investigators (4, 5, 19–22) who studied adult patients with SLE.

The results of this study also showed higher serum sTM levels in JIA patients in comparison with controls. Similar, results have been reported by Conway and Nowakowski (9) and Kotajima et al. (23). On the contrary, Ichikawa et al. (24) reported that plasma levels of sTM were not significantly elevated in RA patients.

On analyzing the observed increased sTM levels in the present study in relation to clinical presentation and the conventional laboratory investigations among SLE patients, sTM correlated significantly and positively with SLEDAI score and with ESR and correlated significantly and negatively with platelet count, Hb and complement (C_3) level. Serum sTM levels were significantly higher in anti-DNA positive than anti-DNA negative patients. SLE activity is associated with thrombocytopenia, anemia, hypocomplementemia, elevated ESR, and positive anti-DNA (4).

The highest sTM levels were seen in patients with both lupus nephritis and cerebritis. Similar

results were obtained by Witte et al. (5) indicating the association of sTM with organ involvement and suggesting that sTM was released from immunologically mediated inflammatory injuries of vascular endothelial cells.

Similar to our results Kiraz et al. (21) reported positive correlation between serum sTM and SLEDAI score. Boehme et al. (17) reported significant correlation between serum sTM and disease activity in SLE as assessed by three established scoring systems: the American College of Rheumatology (ACR), the New York Hospital for Special Surgery (NYHSS), and the Systemic Lupus Activity Measures (SLAM) systems. Horak et al. (25) reported that thrombomodulin best reflects the changing trend in SLE disease activity.

As no specific serological parameter is available to assess disease activity in SLE, soluble serum sTM a new marker of endothelial cell injury and vasculitis has been introduced as a specific serologic parameter to assess disease activity in SLE. Boehme et al. (22) compared serum sTM with established and recent serologic indicators of disease activity in SLE as; intercellular adhesion molecule-1 (ICAM-1), E-selectin, vascular cell adhesion molecule-1 (VCAM-1), IL-2R, IL-6, IL-10, dsDNA, CRP, C₃, IgG, creatinine, ANA, and intermediate filament antibodies together with the evaluation of the clinical disease activity by the SLAM. Correlations of the different serologic SLE disease activity parameters with the SLAM scores revealed the highest significance for serum sTM. This was further confirmed by the intraindividual analysis of follow-up sera. In addition, a moderate correlation could be found for IL-6, IL-10, ICAM-1, CRP, and ESR.

Levels of dsDNA antibodies have been shown to correlate with disease activity and to decrease prior to a relapse of lupus nephritis (15). However, because a substantial group of patients with high levels of dsDNA antibodies do not have manifestations or exacerbations of disease activity (26), this parameter is of limited value in predicting the course of SLE. The same applies to other autoantibodies, to complement levels and to levels of sIL-2R, which is released by activated lymphocytes (15).

Based on current knowledge, sTM is not released on stimulation, but is liberated by damage to endothelial cells (3). Considering immune complex vasculitis and its consequences as a cause of the clinical manifestations of SLE, our results strongly suggest that serum sTM may be a clinically useful serologic marker of vasculitis, reflecting the degree of endothelial cell

damage in SLE. The serum sTM level might prove to be a potential indicator for early treatment. Serum sTM might also be a useful diagnostic tool to allow direct assessment of endothelial cell injury in other forms of vasculitis.

Recent data indicate that the PC-TM anticoagulant mechanism may play an important role in the regulation of the fibrinolytic system and plasmin generation. TM, when complexed with thrombin, supports the conversion of PC to its activated form, whereupon the newly formed serine protease not only suppresses further thrombin formation, but also is reported to enhance the fibrinolytic system by neutralizing plasminogen activator inhibitor-1 (PAI-1). This inhibitor which is present in synovial fluid, provides a major regulatory mechanism for the transformation of plasminogen to plasmin, and presumably therefore serves to protect the joint tissues from destruction. Plasmin, once formed from its precursor plasminogen, may directly degrade extracellular matrix of the joint, or alternatively activate otherwise inactive collagenase that then leads to rapid destruction of collagen-containing tissues (9). This would suggest that excess TM in the presence of adequate thrombin and PC might lead to further destructive processes within the acutely inflamed arthritic joint. However, in addition to several direct anticoagulant properties, recent *in vitro* and *in vivo* studies suggest that sTM may also suppress fibrinolytic activity by accelerating thrombin's inactivation of single-chain urokinase PA (scu-PA) (9,27). Therefore, the alternative scenario would be that sTM directly interferes with plasmin generation, thereby protecting the joint from further deterioration.

Little is known about the role of fibrin deposition in the highly vascular synovial tissue as the proliferating lesion develops into a destructive pannus; however, areas of thrombosis are commonly seen. Lack of TM in the microvasculature caused by either PMN-derived elastase proteolysis or cytokine-induced down-regulation of the surface bound receptor could lead to further fibrin clot formation (28). Mechanisms to enhance TM expression may therefore provide a means to attempt to constrain the overwhelming forces to from intravascular clots in the expanding pannus (9). So in RA TM may play a regulatory role either in fibrin deposition in the inflamed joint and/or in the progression of the inflammatory process (9).

Ichikawa et al. (24) found that sTM levels in the plasma and joint fluid were not significantly elevated in RA patients, although sTM levels in plasma were positively correlated with those in

joint fluid, but the levels showed no connection with systemic inflammatory indices of RA such as ESR, CRP levels. In the joint fluid, TM levels were not correlated with the numbers of neutrophils or monocytes/macrophages associated with articular inflammations. So their results suggested that TM levels in the plasma and joint fluid do not reflect systemic and articular inflammations of RA and suggested that TM molecules in joint fluid are mainly recruited from circulating TM.

Conway and Nawakowski (9) found that synovial fluid from patients with RA had elevated levels of TM that were consistently higher than the plasma levels, indicating local synthesis.

As regards JIA patients in the present study, serum sTM levels were found to be significantly elevated as compared with controls similar to what was reported by Ohdama et al. (4) and Kotajima et al. (23). To our knowledge, this is the first study to be carried out on serum sTM in children and adolescents with JIA (previous studies have been on adults; 4, 9, 23, 24). In JIA patients, sTM correlated significantly and positively to number of joints with active arthritis. sTM also correlated positively and significantly with ESR. Serum sTM was also found significantly higher in CRP-positive than CRP-negative patients. Heidge et al. (29) found that the number of swollen joints is the best single variable which mirrors disease activity in RA. They also found that CRP and ESR have high correlation with disease activity in RA. Similarly Ohdama et al. (4) reported higher values of sTM in active RA than inactive RA and controls.

The results obtained from this study strongly suggest that serum sTM may be a clinically useful serologic marker of disease activity in SLE and JIA. The serum sTM may prove to be a potential indicator for early treatment. Furthermore, serum sTM may prove to be an important marker for vasculitis in general. Follow up of sTM in SLE and JIA patients for longer periods during activity and remission of these diseases is recommended. Measurement of sTM in the synovial fluid and comparing it to serum level in JIA may help to further explore the mechanism of its production as well as its role in the inflamed joint.

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