Soluble adhesion molecules ICAM-1 and E-selectin in juvenile arthritis: Clinical and laboratory correlations

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Abstract

Objective

To determine serum and synovial fluid (SF) concentrations of soluble intercellular adhesion molecule-1 (ICAM-1) and E-selectin (E-sel) in patients with active juvenile idiopathic arthritis (JIA) and in paediatric controls and correlate them with clinical and laboratory variables.

Methods

Total of 30 JIA patients were evaluated: 15 with polyarticular disease course (JIA-poly) and 15 with oligoarthritis (JIA-oligo). Paediatric age-matched control groups consisted of 11 Henoch-Schönlein purpura (HSP) and 10 febrile patients (FC) and 28 healthy children (HC). Current medication, the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and full blood count (FBC) were recorded. Soluble ICAM-1 and E-sel in serum and SF were measured by a sandwich ELISA kit.

Results

In the JIA-poly group the concentration of ICAM-1 was significantly higher than in healthy ($p < 0.01$), but not febrile controls. Both ICAM-1 and E-selectin correlated with the active joint count ($p < 0.01$). In 13 JIA patients no correlation was found between SF ICAM-1 and E-sel levels and the SF leucocyte counts. No significant differences were seen in the disease control and JIA-oligo groups compared to HC. A significant negative correlation with age was observed for the group as a whole (ICAM-1: $p < 0.05$, E-sel: $p < 0.01$); E-sel correlated with the leucocyte and thrombocyte counts ($p < 0.01$), and both molecules with CRP ($p < 0.05$) and with each other ($p < 0.01$).

Conclusion

A high concentration of soluble ICAM-1 in JIA patients with polyarthritis is reported here for the first time. None of the patients showed signs of infection or vasculitis, where generalised endothelial activation could be its main source. Our finding of correlations between both ICAM-1 and E-sel levels and joint counts supports the hypothesis of their synovial origin. ICAM-1 and E-sel could serve as a marker of aggressive disease, but their predictive value needs to be further studied.

Key words

Juvenile chronic arthritis, E-selectin, intercellular adhesion molecule-1.

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Introduction

Adhesion molecules, a large group of cell-surface proteins, mediate wide variety of biological processes including intercellular interactions involved in leucocyte traffic and migration, cell activation and angiogenesis. Their role in pathogenic mechanisms of chronic inflammatory diseases has been recently reviewed (1-3). Up-regulation of adhesion molecule production and/or cell surface expression on endothelial cells and leucocytes upon stimulation with inflammatory mediators enhances recruitment of inflammatory cells into tissues. Increased tissue expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin (E-sel) has been described in various inflammatory conditions including rheumatoid synovitis (4-6). Reduction of synovial expression of VCAM-1 and E-selectin and consequent decrease in inflammatory infiltration after treatment with certain anti-rheumatic drugs illustrates their important role in disease pathogenesis (7, 8).

Soluble forms of these molecules, generated through their proteolytic cleavage from cell surface ("shedding") are detectable in biological fluids. Although these soluble adhesion molecules retain biological activity, their physiological function is not yet fully elucidated (9). E-selectin is exclusively expressed on activated endothelium and therefore the concentration of its soluble form is believed to reflect the extent of endothelial cell activation. The measurement of circulating soluble ICAM-1 is considered to be less specific for endothelial cell activation as ICAM-1 is present both constitutively and is inducible on a variety of cell types including endothelial cells, leucocytes and fibroblasts (2). In RA patients increased levels of soluble ICAM-1 as well as E-selectin were found in both synovial fluid and blood samples (10-15).

In children the concentration of soluble adhesion molecules has been studied in vasculitic disorders (Kawasaki disease, Henoch-Schönlein purpura, systemic lupus erythematosus) and in juvenile idiopathic arthritis (JIA) (16-21). When the different subtypes of JIA were examined, concentrations of blood soluble ICAM-1 and E-selectin were found only in patients with systemic disease, with conflicting results in the clinical and laboratory correlations.

We studied levels of soluble E-sel and ICAM-1 in the serum (and synovial fluid where available) of patients with a polyarticular course of juvenile arthritis and compared these results to the results found in patients with oligoarthritis, other paediatric diseases and healthy controls. We then correlated the ICAM-1 and E-selectin results with clinical and laboratory variables of disease activity.

Materials and methods

Subjects

A total of 30 children (mean age 10 yrs, range 1-18) who fulfilled the criteria for juvenile idiopathic arthritis (22) were investigated. All patients had active synovitis at the time of evaluation. For the purpose of the study they were divided according to their disease course into 2 groups: 15 patients with polyarthritis of different JIA onset types (JIA-poly) [polyarticular RF- (n = 11), polyarticular RF+ (n = 2), extended oligoarticular (n = 1), entezopathy-related (n = 1)] and 15 patients with oligoarthritis (persistent oligoarticular JIA) (JIA-oligo). The mean active joint count in the 15 patients with JIA-poly was 7.5 (range 4-16) and the mean active joint count in the 15 patients with JIA-oligo was 1.5 (range 1-4) (Table I). Active synovitis was defined as the presence of intra-articular swelling or limitation in the range of joint movement with pain or tenderness. At the time of evaluation, the majority of the JIA-oligo patients were receiving non-steroidal antiinflammatory drugs (NSAID) only; in the JIA-poly group, in addition to NSAID 10 patients were receiving methotrexate, 4 prednisone and 2 other second-line agents.

Paediatric age-matched disease control groups (Table I) consisted of 11 acute-onset Henoch-Schönlein purpura patients (HSP) and 10 children with acute febrile diseases (mostly respiratory and gastrointestinal infections) who had experienced at least one fever spike over

Table I. Main clinical and laboratory characteristics of the study groups.

Study group	No.	Age (yrs)*	Disease duration (yrs)*	Active joint count*	ESR mm/h*	CRP mg%*	ICAM-1 ng/ml#	E-sel ng/ml#
JIA-oligo	15	8 (1-16)	1.6 (0.2-4)	1.5 (1-4)	34 (1-150)	2.5 (0-12.1)	317 ± 26	49 ± 10
JIA-poly	15	12.5 (3-18)	3.7 (0.2-11)	7.5 (4-16)	52 (6-138)	8.1 (0.1-22.4)	395 ± 26	65 ± 7
HSP	11	8 (3-17)	-	-	17 (2-47)	0.9 (0-2.7)	320 ± 33	56 ± 13
FC	10	5 (1-16)	-	-	32 (3-71)	2.9 (0.7-5.1)	314 ± 46	65 ± 17
HC	28	12 (1-18)	-	-	-	-	289 ± 22	59 ± 6

HC: healthy children, FC: febrile children, JIA-poly, oligo: juvenile idiopathic arthritis polyarticular, oligoarticular, HSP: Henoch-Schönlein purpura.
*Mean values (range); #Mean age-adjusted values ± SE.

38°C within 24 hours prior to the time of examination (FC). The healthy control group (HC) comprised of 28 children in whom routine blood tests were performed for other reasons. Patients were recruited from paediatric rheumatology and general outpatient clinics as well as from the inpatient department of the Department of Paediatrics and Adolescent Medicine, General Faculty Hospital, Prague, between the spring of 1998 and the winter of 1999. In the patient groups laboratory data on the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) (Table I) and full blood count (FBC) (data not shown) were collected prospectively. In 13 patients (9 JIA-oligo, 4 JIA-poly) joint aspiration (knee joint) was performed within one hour of obtaining the blood sample for adhesion molecule measurments. The synovial fluid total leucocyte cell count (cells/mm^3) and differential count were routinely obtained.

Laboratory examinations

Serum and heparinized SF supernatant samples were separated following centrifugation within 3 hours from venepuncture/joint aspiration and stored at -80°C until tested. ICAM-1 and E-selectin concentrations were measured using sandwich ELISA kit according to the manufacturer's instructions (R&D Systems Europe, Abingdon, UK). For each assay a spectrophotometric signal versus known standard concentrations curve was plotted and used for determination of sample concentrations. For ICAM-1 and E-selectin only adult reference range data were provided by kit manufacturers obtained from a panel of sera from 130 apparently normal male and female donors.

Statistical analysis

Kruskal-Wallis analysis of variance was used for assessing differences in adhesion molecule concentration among different study groups. Adhesion molecule values were age-adjusted using analysis of covariance. Correlations with laboratory and clinical variables were assessed using non-parametric rank correlation coefficient (Spearman's r), a p value < 0.05 was considered statistically significant. Differences in paired serum/SF samples were tested using the Wilcoxon rank test, the correlation of adhesion molecule concentrations in the two compartments was assessed by Spearman's test.

Results

A significant negative correlation with age was found for both soluble ICAM-1 ($p < 0.05$, $r = -0.265$) and E-sel levels ($p < 0.01$, $r = -0.419$) in all groups investigated. The correlation was even more prominent when JIA-poly and febrile controls were excluded (ICAM-1: $p < 0.01$, $r = -0.46$, E-sel: $p < 0.001$, $r = -0.61$) (Fig. 1a, 2a). To obtain a higher accuracy of the results age-adjusted means of adhesion molecule

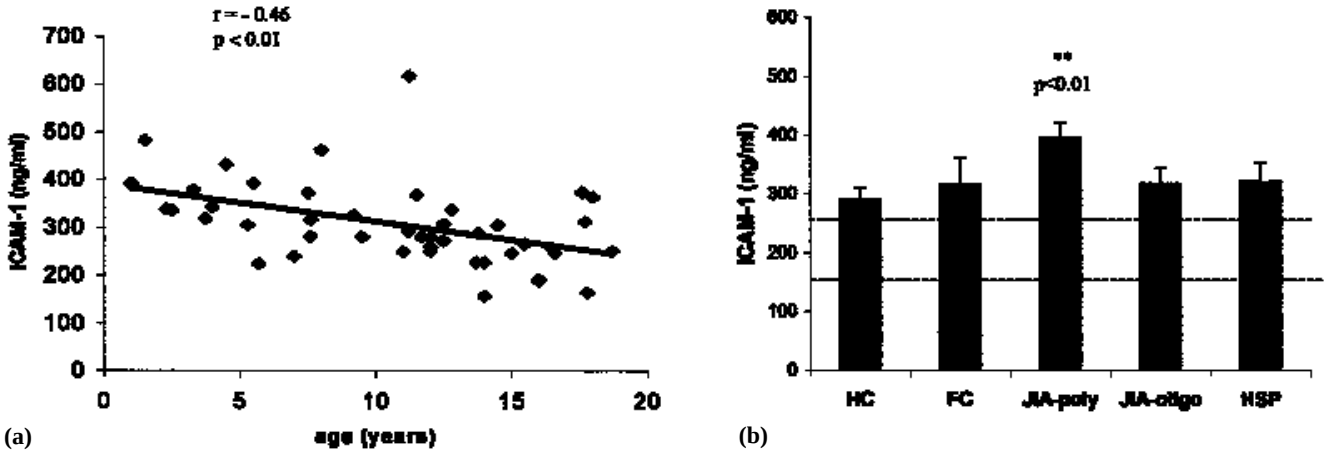

Fig. 1. (a) Relationship of ICAM-1 levels with age; **(b)** ICAM-1 in individual study groups (age-adjusted mean ± SE). HC:healthy children; FC: febrile children; JIA-poly, oligo: juvenile idiopathic arthritis polyarticular, oligoarticular; HSP:Henoch-Schölein purpura. Adult reference range ± SD:163 - 259 ng/ml.

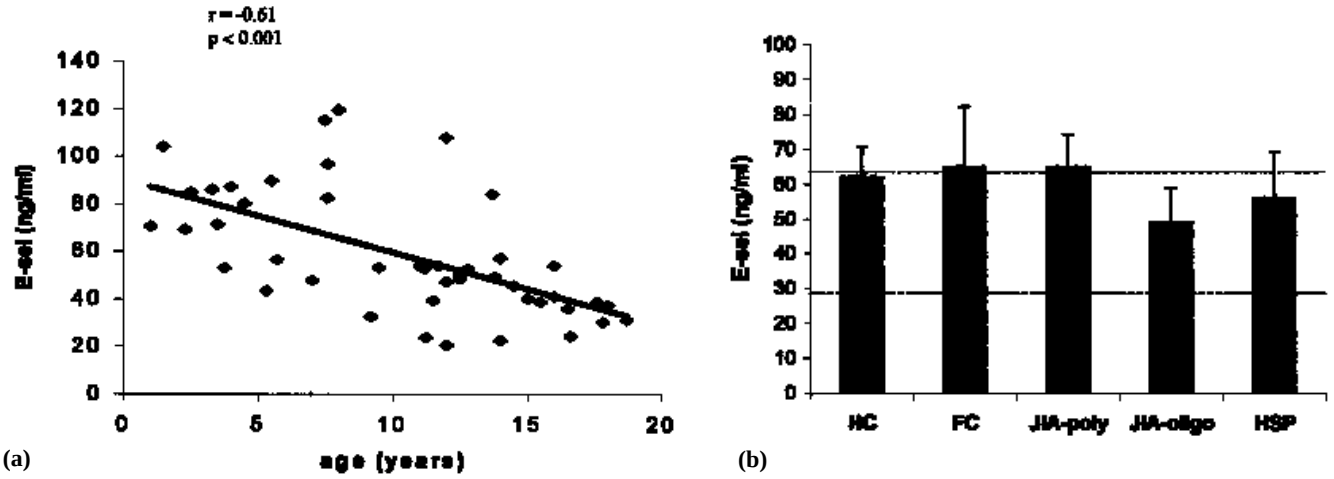

Fig. 2. **(a)** Relationship of E-selectin with age; **(b)** E-selectin in the individual study groups (age-adjusted mean ± SE). Abbreviations as in Fig. 1. Adult reference range ± SD: 29 - 63 ng/ml.

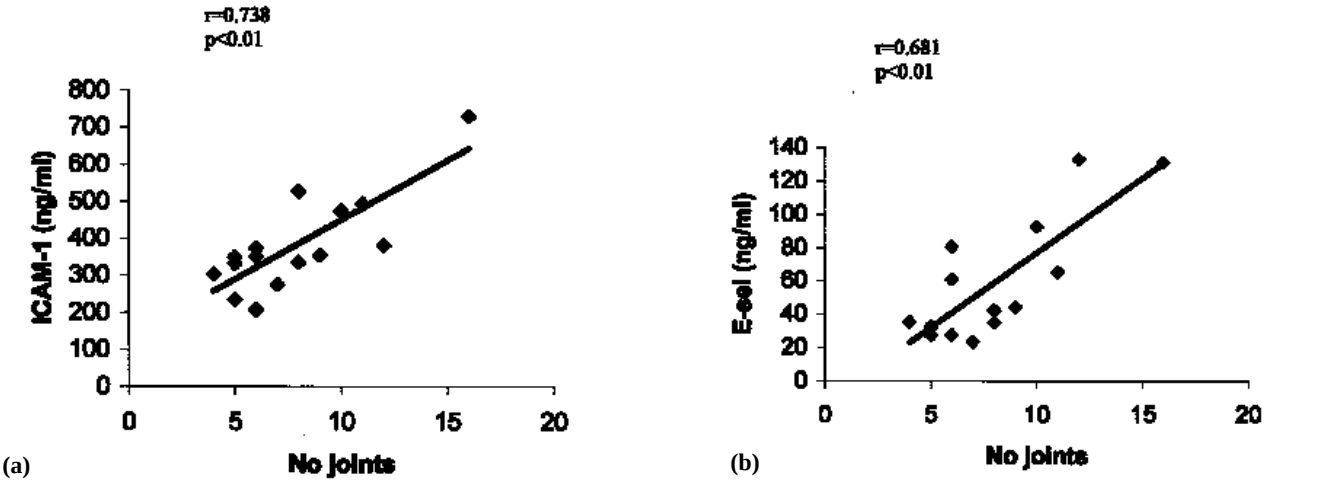

Fig. 3. **(a)** Relationship of ICAM-1 with the number of active joints in the JIA-poly group; **(b)** relationship of E-selectin with the number of active joints in the JIA-poly group. No. of joints: the number of joints with active synovitis at the time of evaluation.

concentrations were used for group comparisons.

Serum concentrations of soluble ICAM-1 and E-selectin

The mean serum concentration of soluble ICAM-1 in the JIA-poly group (395 ± 26 ng/ml) was statistically significantly higher ($p < 0.01$) than the mean ICAM-1 concentration seen in healthy children (289 ± 22 ng/ml), however, the difference was not significant when compared to the means of the disease control groups (FC: 314 ± 46 ng/ml, HSP: 320 ± 33 ng/ml). E-sel concentrations in patients with polyarticular JIA (65 ± 7 ng/ml) did not differ significantly from the levels seen in the healthy controls (59 ± 6 ng/ml). In comparison to the patients with polyarticular JIA, when we examined JIA-oligo group, we did not find any significant difference in the mean concentration of soluble ICAM-1 (317 ± 26 ng/ ml) and E-sel (49 ± 10 ng/ml) as compared to either healthy children or to the disease control groups (Fig. 1b, 2b).

Correlations with clinical and laboratory variables

We next correlated the levels of soluble adhesion molecules with measures of disease activity (Table I). There was a statistically significant correlation of both soluble molecule levels with the active joint count in the JIA-poly group ($p < 0.01$) (Fig. 3 a,b). We did not find any correlation between soluble adhesion molecule levels and the disease duration nor with current therapy in JIA patients (NSAID only versus NSAID + second-line therapy) ($p > 0.05$, E-sel: $r = 0.33$, ICAM-1: $r = 0.29$). There was a statistically significant correlation of serum soluble ICAM-1 and E-sel levels with CRP in all JIA and disease control groups ($p < 0.05$). E-sel correlated with leucocyte and thrombocyte counts ($p < 0.01$ for both), while ICAM-1 did not. There was no significant correlation found for either molecule with ESR, the erythrocyte counts and hemoglobin concentration. Of note, serum levels of soluble ICAM-1 and E-sel were significantly correlated with each other ($p < 0.01$).

Serum versus synovial fluid (SF) concentrations

SF soluble ICAM-1 levels (501 ± 275

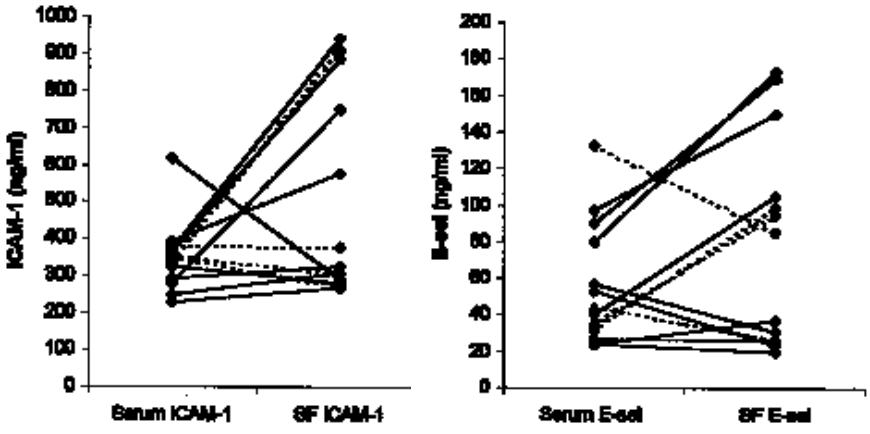

Fig. 4. ICAM-1 and E-selectin concentrations in the serum and synovial fluid paired samples. SF: synovial fluid, - - - - - : patients with polyarthritis.

ng/ml) appeared to be higher than in serum (349 ± 95 ng/ml), but the correlation was not statistically significant ($p > 0.05$, $r = 0.286$). E-selectin concentrations in SF (80 ± 57 ng/ml) did not differ significantly from the serum samples (57 ± 34 ng/ml) ($p > 0.05$, $r = 0.495$). Differences in individual paired samples assessed by the Wilcoxon rank test were also not statistically significant. Nevertheless a more prominent elevation of SF concentrations of both molecules was seen in 4/9 oligoarthritis and 1/4 polyarthritis patients (Fig 4). Neither of the adhesion molecule SF concentrations correlated with the SF total leucocyte count (mean 17.5, range 2.2 - 42.7 cells/mm^3) ($p > 0.05$, E-sel: $r = -0.084$, ICAM-1: $r = 0.150$).

Discussion

We have for the first time demonstrated that in children with polyarthritis the serum concentration of soluble ICAM-1 is increased when compared to the levels seen in healthy children. Our findings are similar to those of studies in adult rheumatoid arthritis (RA), where increased levels of this molecule were found (10-13). However, our results differ from the results of two previous studies in children where elevated serum soluble adhesion molecules were found in patients with systemic-onset JIA but not in those with polyarticular disease (20, 21).

Prior to our study serum soluble adhesion molecules had been studied in a total of 58 children with JIA. Bloom *et al.* evaluated serum concentrations of ICAM-1, ICAM-3, VCAM-1, L-selectin and E-selectin (20), while De Benedetti *et al.* looked at E-selectin, P-selectin and ICAM-1 (21). Both groups found increased serum levels of ICAM-1 and E-selectin in the systemic subgroup of JIA patients only. In our study systemic onset patients were not included to prevent the influence of their expected high levels on the final results. It is difficult to comment on this discrepancy. Bloom *et al.* did not find a correlation between joint counts and adhesion molecule concentrations in the patients investigated (6 systemic, 6 polyarticular, 4 pauciarticular), but they did not show data on either disease activity measures or joint counts, having stated that all had active disease in terms of at least one joint with active synovitis present at the time of evaluation (20). In our polyarthritis group the lowest active joint count of 4 was present in one patient only; the remaining 14 patients had between 5 and 16 active joints. Non-specific inflammatory parameters were high in the majority of the patients. De Benedetti *et al.* investigated 10 patients with seronegative polyarticular JIA, but since they did not find any significant difference in terms of soluble adhesion molecules when compared to healthy controls, they did not show or analyse their clinical data, which prevented further comparisons to our study group (21).

Our findings of a significant correlation between E-selectin levels and non-specific measures of inflammation (ESR, leucocyte and thrombocyte counts) are in agreement with previous findings (20). In systemic disease no correlation with laboratory data, the presence of systemic signs (fever), or current medication was found, but both ICAM-1 and E-selectin levels correlated with the soluble tumor necrosis factor receptor 2 (TNFR2) concentration (21). Our finding of a negative correlation of both circulating molecule levels with age is in agreement with others (16,18, 20) and stresses the importance of age-matched controls in such studies.

It is interesting to speculate on the source of circulating adhesion molecules. Carson *et al.* found higher synovial fluid than serum concentrations of E-selectin, leading to the hypothesis that activated synovial vessel endothelium is the main source of soluble E-selectin. In addition, as these authors demonstrated a correlation of synovial fluid E-selectin and synovial fluid leucocyte counts, they speculated that expression of this molecule on synovial endothelium may lead to leucocyte migration into the joint cavity (14). The source of circulating ICAM-1 levels is more controversial, as one group found increased synovial fluid ICAM-1 levels as compared to serum levels (10) while the reverse was observed by others (11). Studies by a third group led to the conclusion that synovial endothelium was the major source of SF while serum soluble ICAM-1 were likely to be derived from both synovial endothelium and additional sources (12).

Interpretation of the comparison of synovial fluid versus serum ICAM-1 and E-selectin levels was even more difficult. Based on adult RA data (10, 14), we had expected to find higher SF than serum levels and a correlation of synovial fluid soluble adhesion molecules and SF leucocyte counts. We did find a tendency for SF ICAM-1 to be higher than in the paired sera, but the difference did not reach statistical significance, and we did not find a correlation with the SF leucocyte count. There are many possible explanations for these unexpected findings. The group of patients in whom the SF level was available was not a homogeneous group

as seen in adults (9 patients had oligoarthritis and 4 had polyarthritis). There was also a wide variability in disease duration, ranging from 2 months to 6 years. The small number of patients in each group did not allow us to make comparisons, but in the oligoarthritis group there seemed to be a higher tendency towards a more prominent elevation of synovial fluid concentrations of both molecules than in polyarthritis patients, possibly illustrating a more locally active disease process. Sample handling factors and the possible role of SF proteases appear unlikely to have influenced the results (11). Lastly, adhesion molecules may bind to counterreceptor bearing cells and therefore a significant and variable proportion of circulating soluble adhesion molecules may not be measured by the current assay methods (9).

Current evidence suggests that higher circulating levels of ICAM-1 and/or E-selectin are seen in patients with active disease, both RA (10-15) and JIA (20, 21), and correlate with inflammatory cytokine production (mainly TNF-) (13, 21) and the presence of secondary vasculitis (23). Both extra-articular and synovial endothelial activation are likely to be a source of their circulating pool, but their proportion is not known. The importance of the systemic vascular endothelium as the major source of circulating soluble adhesion molecules is suggested by the demonstration that children with febrile illness or acute vasculitis of HSP had levels similar to those seen in patients with polyarticular JIA. As these patients did not show any extra-articular features of systemic disease (fever, vasculitis, infection) at the time of evaluation, it is likely that neovascularised proliferating synovium is another important source of soluble ICAM-1 and E-selectin. The differences in their concentration in serum and synovial fluid could be explained by the different passage of shed molecules from the synovial interstitium into the blood and SF (12).

We have shown that patients with active polyarticular JIA have increased levels of circulating soluble ICAM-1 compared to healthy paediatric controls. It is not clear whether this originates from hypertrophic, highly vascularised synovium, as supported by the correlation with active joint counts, or from the systemic release. Circulating ICAM-1, and possibly also E-selectin measurements could be a marker of more aggressive joint disease, but their predictive value needs to be further studied.

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