# Circulating proangiogenic molecules PIGF, SDF-1 and sVCAM-1 in patients with systemic lupus erythematosus

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**ABSTRACT. Serum concentrations of three angiogenic cytokines: vascular endothelial growth factor (VEGF), stromal cell-derived factor-1 (SDF-1) and placental growth factor (PIGF) and soluble vascular cell adhesion molecule 1 (sVCAM-1), were investigated in the serum of 61 patients with systemic lupus erythematosus (SLE) and 20 healthy subjects. The possible association between serum levels of these proteins and SLE activity, as well as correlation between the concentrations of cytokines were also analysed. All of these factors were detectable in all SLE patients and the healthy control group. The median concentration of VEGF was higher in active SLE (386 pg/mL) than in inactive disease (327 pg/mL) or in the control group (212 pg/mL, $p < 0.004$). The median serum level of SDF-1 was higher in SLE patients (1 814 pg/mL) than in the control group (1 507 pg/mL, $p < 0.02$). The median concentration of PIGF was higher (14 pg/mL) in SLE patients than in the control group (12 pg/mL, $p = 0.03$), and particularly in active disease (17 pg/mL) as compared to the inactive phase (13 pg/mL, $p = 0.01$). The correlations between the levels of cytokines examined and clinical features, laboratory abnormalities and the type of treatment were also analysed. We found a positive correlation between serum concentrations of PIGF and SLE activity according to SLAM score ($p = 0.33$, $p = 0.13$).**

**Keywords:** SLE, disease activity, angiogenesis, VEGF, sVCAM-1, SDF-1, PIGF

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune connective tissue disease that is characterised by immune dysregulation. The clinical spectrum of the vascular injury is wide and there is no doubt that endothelial activation and damage are central to the pathogenesis of the vascular disease seen in SLE [1]. Vascular endothelial growth factor (VEGF) is a crucial mediator of vascular hyperpermeability, angiogenesis and inflammation, processes intimately involved in tissue repair. VEGF exerts its biological effects upon binding to two high-affinity receptors of tyrosine kinases VEGFR-1 and VEGFR-2, expressed predominantly on endothelial cells but also on some non–endothelial cells including neutrophils, macrophages, pericytes and stromal cells. Whether VEGF signalling in these cells is functionally relevant in tissue repair is currently unknown [2]. Most of endothelial VEGF signalling described to date is largely mediated via VEGFR-2. The function of VEGFR-1 is less clear.

The placental growth factor (PIGF) is a member of the vascular endothelial growth factor family. It has been shown to play an important role in promoting adult neoangiogenesis associated with pathological events, such as ischemia, inflammation, tumor growth and wound healing [3-5].

Stromal cell-derived factor (SDF-1), also known as chemokine CXCL 12, is involved in the homeostatic and inflammatory traffic of leukocytes. Binding of SDF-1 to glycosaminoglycans on endothelial cells (EC) is supposed to be relevant to the regulation of leukocyte diapedesis and neoangiogenesis during inflammatory responses [6]. Among the chemokines, SDF-1 is unique because it binds to one single chemokine receptor, CXCR4 [7, 8]. Through specific interactions with the CXCR4 and VEGFR-2 receptors, SDF-1 and VEGF, respectively, contribute to an increase in the recruitment of progenitor cells from the bone marrow to the peripheral blood, thereby leading to formation of the new vessel at the ischemic sites [9].

Vascular cell adhesion molecule (VCAM-1) is a member of the immunoglobulin supergene family (IGSF), one of three groups of adhesion molecules. These molecules enable leukocyte adhesion and rolling along endothelial cell surfaces, and control migration of leukocytes into the inflamed tissues. Adhesion molecules are also important in cell-cell interactions of lymphocyte co-stimulation, cytotoxicity and apoptosis [10]. VCAM-1 is a type I transmembrane glycoprotein that is generally not expressed by the normal endothelium but is induced by inflammation [11]. VCAM-1 is also expressed on antigen-presenting cells

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(APC), and binds very late activation antigen 4 (VLA4) on T cells. This binding ensures stabilization of the synapsis between APC and T cell and leads to optimal responses [12]. VCAM-1 needs to be induced on the surface of endothelial and other cells by inflammatory cytokines, especially tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interferon-γ (IFN- γ) [10].

In the present study, we measured the serum concentrations of VEGF, sVCAM-1, SDF-1, and PIGF, in patients with SLE using ELISA. Serum levels of these proteins were also correlated with the disease activity and clinical and laboratory abnormalities.

## PATIENTS AND METHODS

The study involved 61 SLE patients (56 females and 5 males), aged 21-66 years (mean 39.2 years). The diagnosis was based on the revised criteria of the American College of Rheumatology [13]. Twenty-one patients had never been treated with steroids or any other immunosuppressive agents. Forty patients were being treated with prednisone at a dose of 5-30 mg/day during the blood collection, and seven of them also with azathioprine at a dose 50-150 mg/day at some time during the course of the disease. What is important is that none of them had been treated for at least four weeks before the study. The patients' characteristics are shown in *table 1*. Disease activity was evaluated on the day of blood sample collection for cytokine analysis according to the method described by Liang *et al*. [14]. The system of Systemic Lupus Activity Measure (SLAM) includes 24 clinical manifestations and eight laboratory parameters. Parameters of immune function are not included. The maximum score of this system is 84 points. We assumed a score of 0-15 points to be inactive disease and a score of over 15 points as active disease. According to this definition, in our group of patients, 17 had active and 44 inactive disease. Control serum was obtained from 20 healthy volunteers, 18 women and two men, aged from 18 to 65 years (mean 38 years). Each patient underwent thorough physical examination performed by one of the authors (ER). This project was performed in accordance with the Helsinki Declaration. Informed consent was obtained from all patients participating in the study. The local Ethics Committee approved the project.

## CYTOKINE DETERMINATION

Venous blood samples were collected into pyrogen-free tubes at the time of clinical assessment. They were allowed to clot at -4°C for 1 hour and the centrifuged at 2 000 g for 10 min. The serum obtained was divided into aliquots and stored at -80°C until assayed for VEGF, sVCAM-1, PIGF, and SDF-1. The detection of serum cytokine levels was performed using ELISA sandwich kits. The kits were obtained from R&D Systems Inc, Minneapolis, USA. The cytokine serum concentrations were analysed in accordance with the manufacturer's instructions using an ELISA reader at 492 nanometers. In each assay, the appropriate recombinant human cytokine was used to generate the standard curve. The procedure has been described in detail elsewhere [15, 16].

**Table 1**
Clinical and laboratory characteristics of SLE patients

| Symptoms | Number of patients | % |
|---|---|---|
| Total | 61 | 100.0% |
| Age (years) mean (range) | 39.2 (21- 66) | |
| Sex (male/female) | 5/56 | 8.2%/91.8% |
| Active / Inactive | 17/44 | 27.9%/62.1% |
| Immunodiffusion (dsDNA antibodies) | 6 | 9.8% |
| RBC (< 4.0 x $10^6 mm^3$) | 23 | 27.7% |
| HGB (< 14.0 g/dL) | 49 | 80.3% |
| HCT (< 40.0%) | 48 | 78.7% |
| Leukopenia WBC (< 4.0 x $10^3 mm^3$) | 25 | 41.0% |
| Lymphocytes (< 1.0 x $10^3 mm^3$) | 18 | 29.5% |
| Thrombocytopenia platelets (< 130 x $10^3 mm^3$) | 10 | 16.4% |
| Raised ESR (≥ 25 mm/h) | 24 | 39.4% |
| $C_3$ < 0.9 | 20 | 32.8% |
| $C_4$ < 0.1 | 17 | 27.9% |
| C reactive protein (≥ 6.0 mg/L) | 4 | 6.6% |
| Gammaglobulins < 12% | 24 | 39.4% |
| AST > 40 U/L | 5 | 3.3% |
| ALT > 40 U/L | 4 | 6.6% |
| Antinuclear antibodies ANA | 54 | 88.5% |
| APTT (≥ 40.0 s) | 4 | 6.6% |
| Arthritis | 52 | 85.2% |
| Skin symptoms | 28 | 45.9% |
| Neurological symptoms | 6 | 9.8% |
| Hematological symptoms | 43 | 70.5% |
| Renal disorder | 3 | 4.9% |
| Immunosuppressive treatment with steroid and/or cytotoxic agents during the study | 40 | 65.6% |

Standards, as well as samples, were evaluated as duplicates and the inter-assay variations were shown to be within the range given by the manufacturer. Assay sensitivity was 9.0 pg/mL for VEGF, 7.0 pg/mL for sVCAM-1 and PIGF, and 18 pg/ml for SDF-1.

## STATISTICAL ANALYSIS

For the statistical analysis of the data, the range of measured variables is given (min-max). Mean arithmetic value (x), median (Me) and standard deviation (SD) were also calculated. The Shapiro-Wilk's test was used to evaluate the distribution. The comparison of three mean values was performed in order to estimate the possible statistically significant differences between these groups and the combined variance within the analysed groups. In case of the existence of these differences, the comparison for all possible pairs was performed. In this way, the analysis between two compared groups was possible. The differences in mean values in three groups were evaluated with the Kruskal-Wallis test or by the analysis of variance. The comparison of variable values in two groups was performed depending on the distribution of features of the Mann-Whitney test, or the test for two means for independent samples or the Cochran-Cox or Tukey test. The correlation between features was evaluated using the Spearman rank coefficient p. Comparisons and correlations were considered significant when $p < 0.05$.

## RESULTS

In the group of 61 SLE patients, 17 were in an active and 44 in an inactive stage of the disease according to the SLAM score. The serum concentrations of VEGF, PIGF, sVACAM-1 and SDF-1 in SLE patients and in healthy persons are shown in *table 2*. All of the cytokines were detectable in all patients with SLE and in all healthy donors.

In active SLE, the median serum concentration of VEGF was 385 pg/mL and was higher than in the inactive disease (327 pg/mL) and in control group (212 pg/mL, $p < 0.004$). The median serum level of SDF-1 was higher in the SLE patients (1814 pg/mL) than in the control group (1 507 pg/mL, $p < 0.02$). However, there was no statistically significant difference between active SLE (1 933 pg/mL) and inactive disease (1 807 pg/mL, $p > 0.05$). The serum concentration of PIGF was 14 pg/mL in all SLE patients and it was statistically significantly higher than in the control group (12 pg/mL, $p < 0.003$). It was higher in active (17 pg/mL) compared to inactive disease (13 pg/mL, $p = 0.01$) and in the control group (12 pg/mL, $p = 0.005$). Similarly, serum levels of sVCAM-1 were higher in SLE patients (1 492 pg/mL), particularly in active SLE (1 548 pg/mL) than in the inactive disease (1 533 pg/mL, $p = 0.002$) and in the control group (883 pg/mL, $p = 0.0001$).

We also analysed serum angiogenic factor levels and compared them with the selected clinical and laboratory parameters of the patients with SLE (*table 3*). In the group of 61 patients, 40 were treated with steroids and/or cytotoxic agents. However, the levels of all four angiogenic factors were not statistically different in either group. Moreover, the levels of PIGF were lower in patients with the median level of C3 > 0.9 mg/L (14.9 pg/mL) than in the patients with C3 < 0.9 mg/L (11.3 pg/mL) ($p = 0.03$). Similarly, the median level of PIGF was lower in patients with C4 > 0.1 mg/L (11 pg/mL) than in patients with C4 < 0.01 mg/L (15 pg/mL) ($p = 0.01$). The median level of PIGF was also lower in those patients with neurological symptoms (median 11 pg/mL) than in the patients without neurological symptoms (median 14 pg/mL) ($p = 0.05$). We found a positive correlation between the PIGF serum concentration and the SLE SLAM activity score ($\rho = 0.33$, $p = 0.01$) *(figure 1)*. Correlations between SLE activity and serum levels of VEGF and SDF1 were not statistically significant. We also analysed the relationship between serum concentrations of particular angiogenic factors. The statistically significant positive correlations are shown in *figure 2*. We found significant positive correlations between serum levels of VEGF and PIGF ($\rho = 0.3$, $p = 0.03$), VEGF and SDF 1($\rho = 0.25$, $p = 0.05$), and SDF1 and PIGF ($\rho = 0.46$, $p = 0.0003$).

**Table 2**
Serum levels of VEGF, sVCAM, PIGF, SDF-1 in patients with SLE and the control group
(values of VEGF, PIGF and SDF1 in pg/mL, sVCAM in ng/mL)

| Factor | All SLE n = 61 (a) | Active SLE n = 17 (b) | Inactive SLE n = 44 (c) | Control group n = 20 (d) | Statistically significant comparison |
|---|---|---|---|---|---|
| **VEGF** | 431.9 ± 311.6 | 391.4 ± 209.4 | 448.8 ± 346.1 | 202.5 ± 117.6 | (a)-(d) p = 0.001 |
| **± s** | 335.7 | 385 | 326.7 | 211.8 | (b)-(c)-(d) p =0 .004 |
| **Me** | (26.1-1438.4) | (62.5-729) | (26.1-1438.4) | (13.4-399) | (b)-(d) p = 0.006 |
| **Range** | | | | | (c)-(d) p = 0.002 |
| **sVCAM** | 1 560 ± 671.7 | 1 568.4 ± 657.6 | 1 539.9 ± 725.2 | 852.3 ± 206.9 | (a)-(d) p = 0.001 |
| **± s** | 1492 | 1548 | 1533 | 883 | (b)-(c)-(d) p = 0.001 |
| **Me** | (662-3 428) | (662-3 428) | (698-3196) | (382-1 196) | (b)-(d) p = 0.0002 |
| **Range** | | | | | (c)-(d) p = 0.001 |
| **PIGF** | 14.4 ± 5.4 | 17.6 ± 7.1 | 13,1 ± 3,9 | 11.2 ± 3.6 | (a)-(d) p = 0.03 |
| **± s** | 13.55 | 17.3 | 12.9 | 12.0 | (b)-(c)-(d) p = 0.005 |
| **Me** | (4.4-32.2) | (7.1-32.2) | (4.4-23.4) | (4.7-17.0) | (b)-(c) p = 0.01 |
| **Range** | | | | | (b)-(d) p = 0.009 |
| | | | | | (c)-(d) p = 0.02 |
| **SDF-1** | 1 794.6 ± 490.4 | 1 789.7 ± 514 | 1 796.7 ± 486.8 | 1 556.4 ± 357.6 | (a)-(d) p = 0.024 |
| **±s** | 1814 | 1933 | 1807 | 1506.5 | |
| **Me** | (490-3589) | (1040-2890) | (490-3589) | (1077-2262) | |
| **Range** | | | | | |

**Table 3**
Serum levels of VEGF, sVCAM, PIGF, SDF-1 in patients with selected SLE symptoms
(values of VEGF, PIGF and SDF1 in pg/mL, sVCAM in ng/mL)

| Symptom | | | VEGF | sVCAM | PIGF | SDF-1 |
|---|---|---|---|---|---|---|
| $C_3$ < 0.9 mg/L | + | ±s | 561.7 ± 378.6 | 1 822.1 ± 675.5 | 15.5 ± 4.4 | 1 811.6 ± 632.7 |
| | | Me | 467.15 | 1 623 | 14.9 | 1 814 |
| | | Range | (71.6-1 438.4) | (944-3 290) | (4.9-25.5) | (490-3 589) |
| | - | ±s | 353.9 ± 248.3 | 1 553.5 ± 782 | 12.8 ± 6.5 | 1 763.1 ± 408 |
| | | Me | 308.7 | 1 339 | 11.3 | 1 734 |
| | | Range | (26.1-960.8) | (662-3 428) | (4.9-32.2) | (1 094-2 890) |
| | p-value | | p = 0.07 | p = 0.13 | p = 0.03 | p = 0.47 |
| $C_4$ < 0.1 mg/L | + | ±s | 494.5 ± 370.1 | 1 798.2 ± 599.4 | 16.0 ± 3.7 | 1 764.8 ± 448.2 |
| | | Me | 450.7 | 1 638 | 15.1 | 1 807 |
| | | Range | (62.5-1 438.4) | (944-3 026) | (11.1-25.5) | (490 -2417) |
| | - | ±s | 408.5 ± 299.6 | 1 550.2 ± 789.9 | 12.8 ± 6.1 | 1 788.1 ± 553.2 |
| | | Me | 316.9 | 1 247 | 12 | 1 729 |
| | | Range | (26.1-1 233.8) | (662-3428) | (4.4-32.2) | (728-3 589) |
| | p-value | | p = 0.43 | p = 0.09 | p = 0.01 | p = 0.46 |
| Neurological symptoms | + | ±s | 280 ± 186.7 | 1 167.3 ± 448 | 10.2 ± 3.5 | 1 641.3 ± 455.6 |
| | | Me | 234.9 | 1 153 | 10.6 | 1 780.5 |
| | | Range | (67.5-525.2) | (662 -1734.0) | (4.4-14.2) | (1 080 -2 083) |
| | - | ±s | 459.9 ± 321.5 | 1604.5 ± 695.1 | 14.8 ± 5.5 | 1 788.4 ± 488.4 |
| | | Me | 373.7 | 1 492 | 14 | 1 795 |
| | | Range | (26.1-1 438.4) | (696-3 428) | (4.9-32.2) | (490-3 589) |
| | p-value | | p = 0.15 | p = 0.16 | p = 0.05 | p = 0.71 |
| Treatment with steroids and immuno-suppressive agents | + | ±s | 408.8 ± 287.5 | 1 598.9 ± 654.4 | 14.9 ± 5.9 | 1 749.2 ± 483.4 |
| | | Me | 316.9 | 1 532 | 14.2 | 1 795 |
| | | Range | (26.1-1 233.8) | (696-3428) | (4.4-32.2) | (490-2 890) |
| | - | ±s | 492.6 ± 373.2 | 1 344.3 ± 613.3 | 12.6 ± 3.9 | 1 774.8± 280.6 |
| | | Me | 381.3 | 1 072 | 12 | 1 821 |
| | | Range | (108.9-1 4384) | (662-3 026) | (7.5-21.7) | (1 210-35 89) |
| | p-value | | p = 0.45 | p = 0.1 | p = 0.01 | p = 0.99 |

## DISCUSSION

Recent studies have indicated the importance of angiogenesis and angiogenic factors in SLE pathogenesis [17-20]. The aim of our investigation was to evaluate serum concentrations of the lesser known angiogenesis-mediating factors (SDF-1, PIGF1) in patients with SLE, and their correlation with disease activity and the presence of some of its clinical symptoms and laboratory parameters. Moreover, we also assessed the concentration of the most well known proangiogenic factor VEGF, which served as the reference point.

Our study has confirmed previous reports demonstrating higher VEGF concentration in SLE patients as compared to patients with inactive disease [18-20]. However, the concentration of another angiogenic cytokine, PIGF, has not been previously determined in SLE patients. Our results indicate that PIGF concentrations are higher in SLE patients (14.2 pg/mL) than in healthy subjects (11.2 pg/mL) (p = 0.03), and also higher in active (17.5 pg/mL) as compared to inactive disease (13.1 pg/mL) (p = 0.01). We have also revealed a positive correlation between the PIGF concentration and SLE activity according to the SLAM classification (p = 0.33, p = 0.01). PIGFF has not been previously determined in SLE patients. This cytokine, being a member of the VEGF family, plays an important role in promoting adult pathophysiological neovascularization, and acts by binding and activating the vascular endothelial growth factor receptor-1 [21, 22]. PIGF enhances monocyte chemotaxis, vascular growth, and bone marrow precursor cell mobilization [23-25]. The observations concerning a direct effect of PIGF on skin fibroblasts that undergo cytokine-mediated migration may indicate a potent role of PIGF in SLE pathogenesis [26]. Moreover, PIGF induces vascular formation directly through the impact on VEGF receptors as well as through the increased VEGF secretion by mononuclear cells [27, 28]. It is worth noting that PIGF is the most potent inducer of PPMG and VEGF production in rheumatoid arthritis [27]. Correlation of the VEGF concentration with PIGF in our study may be an indication that PIGF also stimulates VEGF production in SLE patients.

We have demonstrated higher serum concentrations for two cytokines, SDF1 and VCAM, in SLE patients as compared to healthy subjects. SDF-1 is a key player in postnatal vasculogenesis [28]. Because of specific interaction with the CXCR4 receptor, this chemokine increases the recruitment of progenitor cells from the bone marrow to the peripheral blood, thereby leading to the formation of new vessels at the ischemic sites [9]. The results of experimental studies on New Zealand Black/New Zealand White mice (NZB/NZW) show SDF-1 involvement in SLE pathogenesis [32, 33]. They revealed that peritoneal B1a lymphocytes in lupus-prone NZB/NZW mice are hypersensitive to SDF-1 and IL-10 activity, and that DSF-1 plays a key role in the development of autoimmunity in this mouse model of lupus [29]. B-lymphocyte hypersensitivity in NZB/NZW mice may result from an increased expression of the CXCMG receptor on these cells [29]. The

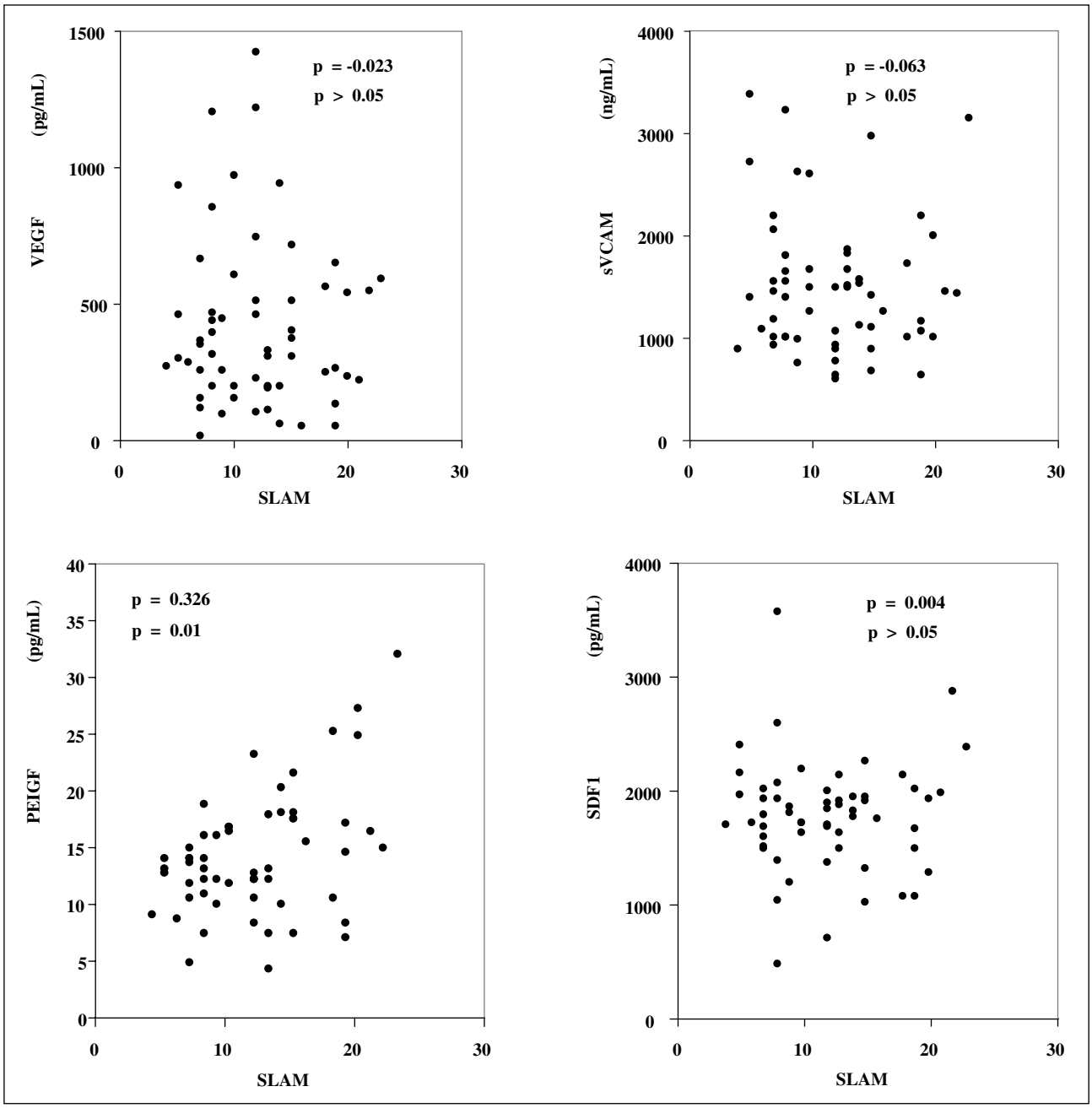


**Figure 1**
Correlations between VEGF, sVCAM-1, PIGF and SDF-1 serum concentrations and SLE activity score.

use of SDF-1 neutralizing monoclonal antibodies preventing the development of autoimmune disease in mice signifies SDF-1 involvement in SLE pathogenesis. Furthermore, SDF-1α affects the production of autoantibody Ig deposition, nephritis and death of these SLE-prone mice [29]. SDX-1α acts also as a pro-inflammatory factor in the pathogenesis of autoimmune arthritis by attracting inflammatory cells to joints and stimulating the differentiation and activation of osteoclasts [30, 31].

The results of our and other experimental studies may indicate the usefulness of therapeutic trials to apply SDF-1 neutralising antibodies in the treatment of SLE in humans.

Vascular cell adhesion molecule-1 (VCAM-1) was the next molecule assessed in our patients. Its concentration was considerably higher in SLE patients than in healthy subjects. A higher serum concentration of this molecule in SLE patients was also reported by other authors [32, 34]. They showed, similarly to our study, a correlation between VCAM-1 concentration and disease activity. Adhesion molecules, including VCAM-1, released into the blood circulation through the activated endothelial cells, are considered to be markers of activation of endothelial cells and leukocytes in a variety diseases, including autoimmune RA and SLE [35, 36].

Summing up, our study has revealed that angiogenic cytokines, VEGF, PIGH, as well as angiogenesis-mediating chemokine SDF-1, and adhesion molecule VCAM-1 can play a significant role in SLE pathogenesis. These factors occur in higher serum concentrations in SLE patients as compared to healthy subjects, and correlate with the disease activity. They may be useful markers for determining disease activity.

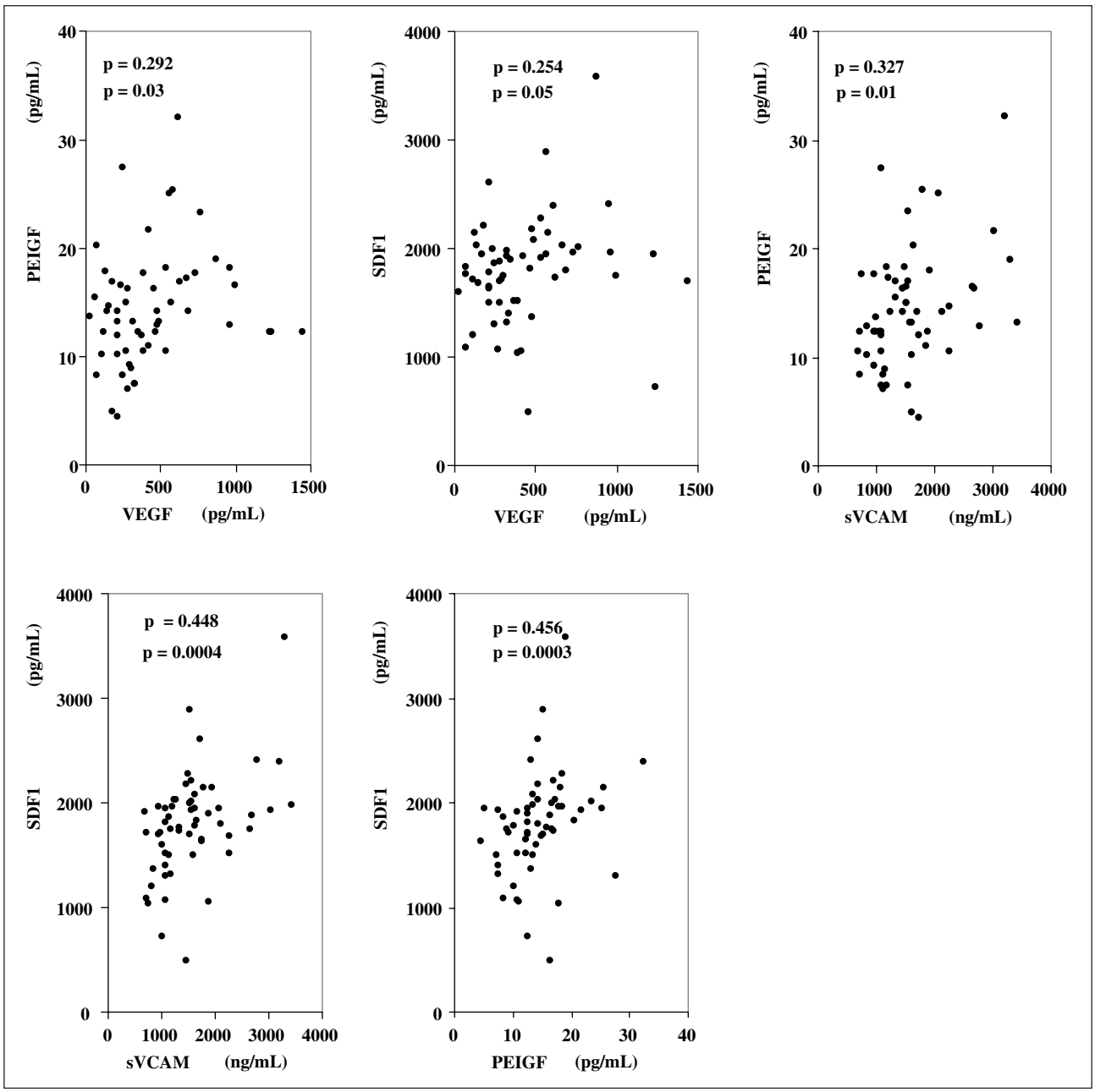


**Figure 2**
Correlations between serum concentrations of investigated proteins.

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