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Serum levels of angiogenic cytokines in systemic lupus erythematosus and their correlation with disease activity

Abstract

We investigated the serum concentration of hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and transforming growth factor beta1 (TGF-beta1) using an enzyme-linked immunosorbent assay (ELISA) in a group of 60 patients with systemic lupus erythematosus (SLE), and 20 healthy controls. We also examined the possible association between the serum concentrations of these factors and certain clinical, laboratory parameters and SLE activity. HGF, VEGF and TGF-beta1 were

detectable in all patients with SLE, and in all normal individuals. bFGF was measurable in 70% of the patients with SLE and in 65% of the healthy controls. The HGF level was higher in active SLE (median 1,019.5pg/ml) than in inactive SLE (median 787.8 pg/ml) ($p < 0.005$) or in the control group (median 847.0 pg/ml) ($p < 0.009$). The level of VEGF in active SLE was also higher (203.5 pg/ml) than in inactive disease (116.1 pg/ml) ($p < 0.05$) or in healthy persons (133.5 pg/ml) ($p < 0.04$). The levels of bFGF and TGF-beta1 were similar for both the active and inactive SLE, and the control group ($p > 0.05$). We found a significant, positive correlation between the levels of HGF and bFGF ($r = 0.268$, $p < 0.04$), HGF and TGF-beta1 ($r = 0.365$, $p < 0.005$) and HGF and VEGF ($r = 0.327$, $p < 0.02$) as well as VEGF and TGF-beta1 ($r = 0.543$, $p < 0.001$). We found a positive correlation between VEGF serum levels and platelet counts ($r = 0.272$, $p < 0.04$), and the TGF-beta1 concentration and platelet count ($r = 0.313$; $p < 0.02$). There was also a positive correlation between HGF serum concentration and the SLE activity score ($r = 0.435$, $p < 0.001$), as well as between the level of VEGF and SLE activity ($r = 0.252$, $p = 0.05$). In conclusion, serum levels of the angiogenic factors HGF and VEGF may be relevant in SLE pathogenesis. Their concentrations seem to be markers of SLE activity.

Full text

INTRODUCTION

The angiogenic process plays a major role in the development of vascular supply under different pathological conditions such as malignancies and non-neoplastic diseases [1-3]. A family of pro- and anti-angiogenic factors tightly regulates angiogenesis. A large number of cytokines have been shown to stimulate angiogenesis under experimental conditions, including vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-beta1), hepatocyte growth factor (HGF) and basic fibroblast growth factor (bFGF) [3-6].

Several angiogenic growth factors are detectable in human serum or plasma especially in pathological conditions, including neoplastic and collagen diseases [7-11]. Some of the angiogenic cytokines may have prognostic value. The VEGF and bFGF serum level was found to be elevated in cancer patients. The literature data indicate that the raised serum level of these cytokines is related to a poor prognosis for patients with non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) [11-15]. The importance

of angiogenic cytokines in the pathogenesis of collagen diseases, and their clinical significance in these diseases, has been less intensively investigated than in neoplastic diseases. Kadono *et al.* measured bFGF among patients with systemic sclerosis (SS) systemic lupus erythematosus (SLE), dermatomyositis (DM) and Raynaud's syndrome [10]. They found detectable levels of this cytokine in these patients. The serum level of VEGF in patients with rheumatoid arthritis (RA), osteoarthritis (OA), SLE and SS was evaluated by Harada *et al.* [9]. The serum concentration of VEGF was significantly higher in patients with RA than in the control group. However, the serum level of this cytokine was not significantly higher than in healthy persons. A similar study, which in SLE, OA and SS was performed by Kikuchi *et al.*, showed a significantly higher level of VEGF in RA, polymyositis/dermatomyositis (PM/DM), and also in SS [16].

The present study focused on the measurement of VEGF, TGF-beta1, bFGF and HGF serum concentration in patients with SLE using an ELISA. The serum levels of these cytokines were correlated with some clinical and laboratory parameters, and disease activity.

PATIENTS AND METHODS

The study group consisted of 60 patients with SLE (55 females and 5 males) and 20 sex- and age-matched healthy volunteers. The median age of the SLE patients was 40 years (range 17-76). The diagnosis of SLE was based on the revised criteria of the American Rheumatism Association [17]. The patients' characteristics are shown in Table 1. The mean duration of the disease was 58 months (range 6 months-21 years). Twenty-five patients had never been treated with steroids or any other immunosuppressive agents. Thirty-five patients had been treated with prednisone for some time during the course of their disease, but only 14 had received this agent during blood collection. Five patients were receiving treatment with prednisone and cyclophosphamide or azathioprine. Patients histories were recorded and physical examination was performed on the day of blood collection. Disease activity was scored according to the method described by Liang *et al.* [18]. Each patient was exaqmined on two separate occasions, 2-4 weeks apart. The system of Systemic Lupus Activity Measure (SLAM) includes 24 clinical manifestations and eight laboratory parameters. The maximum score in this system is 84 points. In our group of patients, the number of points ranged from 9 to 25. In the present study, we considered a score of 0-15 points as inactive disease and a score of over 15 points as active disease. By

this definition, active disease was found in 32 patients while 28 patients had inactive disease. Nine patients in the inactive disease group were receiving treatment with steroids and/or cytotoxic agents and 5 patients in the active disease group. A control group of 20 healthy volunteers was also studied. These comprised 18 women and 2 men, aged from 18 to 65 years (median 38 years).

Each person underwent a thorough physical evaluation by one of the authors (ER). The patients with SLE, and controls showed no clinical signs of infection or neoplastic disease and received non antibiotics or any other medication for at least 4 weeks prior to blood donation. This project was performed in accordance with the Helsinki Declaration. Informed consent was obtained from all patients participating in the study. The project was approved by the local Ethics Committee.

LABORATORY TESTS

In the study group, the following laboratory parameters were analyzed: complete blood cell count (CBC), erythrocyte sedimentation rate (ESR), urinalysis, blood urea, creatinine and fibrinogen levels, C reactive protein (CRP), partial thromboplastin time (PTT), liver function tests (GOT, GPT, bilirubin), immunoglobulins (IgG, IgA, IgM) complement (C_3, C_4), and antinuclear antibodies (ANA). The lupus band test (LBT) was also performed.

SERUM SAMPLING AND CYTOKINE DETERMINATION

Venous blood (5 ml) was collected in pyrogen-free tubes, allowed to clot at 4 °C for 1 hour and centrifuged at 2,000 g for 10 min. The sera obtained were allocated into separate vials and stored at - 25 °C until assayed for cytokines.

The detection of the serum cytokine levels was performed using ELISA sandwich kits employing human anti-VEGF, anti-bFGF, anti-HGF and anti-TGF-beta1 antibodies (R & D Systems Inc, Minneapolis, USA), using horseradish peroxidase detection in accordance with the manufacturer's instructions. The absorption was read at 492 nanometers. The appropriate recombinant human cytokine was used in each assay to generate the standard curve. Standards as well as samples were assayed as duplicates and the interassay variations were shown to be within the range given by the manufacture. Assay sensitivity was 9.0 pg/ml

for VEGF, 1.0 pg/ml for bFGF, 40 pg/ml for HGF and 7 pg/ml for TGF-beta1. The procedure has been described in detail elsewhere [19, 20].

STATISTICAL ANALYSIS

For the statistical analysis of the data obtained, the range of measured variables is given (min-max). Mean arithmetic values (x) and standard deviation (SD) have also been calculated. The Shapiro-Will test was used to evaluate the distribution. The comparison of values of variables in two groups was performed depending on the distribution of features of the Mann-Whitney test, or the test for two means from small samples. In this case, the condition of homoscedasticity was checked using the Fischer test. If the condition of homoscedasticity was not met, the comparison of mean values was done with the Cochran-Cox test. The difference in mean values of the three groups was evaluated with the Kruskal-Wallis test or by an analysis of variance. Then, either the Mann-Whitney test or the Tukey test was performed for an indirect comparison. The correlation between features was evaluated using the Spearman rank coefficient rhô. Comparisons and correlations were considered significant when $p < 0.05$.

RESULTS

In the group of 60 SLE patients, 32 people were diagnosed as having active and 28 with inactive disease according to the Liang *et al.* scoring system [18]. Table 2 shows the results of HGF, bFGF, VEGF and TGF-beta1 serum level measurement in SLE patients and in 20 healthy donors. HGF, VEGF and TGF-beta1 were detectable in all patients with SLE and in all healthy individuals. bFGF was measurable in 42 (70%) patients with SLE and in 13 (65%) healthy persons. The highest HGF concentrations were detected in active SLE patients (median 1,019.5 pg/ml) and the lowest in inactive SLE patients (median 787.8 pg/ml) ($p < 0.005$). The level of this cytokine was also higher in active SLE patients, than in healthy individuals (median 847.0 pg/ml) ($p < 0.009$). In contrast, the levels of HGF in inactive disease and in the control group were not statistically different ($p > 0.05$). Similar differences were observed for VEGF. In active SLE, the median serum concentration of this cytokine was 203.5 pg/ml and in the control group 133.5 pg/ml ($p < 0.04$). The median serum concentrations of VEGF in active SLE was also higher than in inactive disease (116.1 pg/ml) ($p < 0.05$). However, there was no difference between VEGF concentration in inactive SLE and in the control

group ($p > 0.05$). Contrary to HGF and VEGF, the serum levels of bFGF and TGF-beta1 were similar in both active and inactive stage of the disease, as well as in the control group (Table 2). There was no difference in the concentration of these cytokines in active and inactive SLE patients.

We also analyzed the correlation between the skin symptoms and the angiogenic cytokine levels (Table 3). In the group of 30 SLE patients with skin symptoms, 9 patients were being treated with steroids and/or cytotoxic agents and 19 patients had active disease. There was no correlation between skin changes and SLE activity or treatment. The median HGF level was higher in SLE patients with skin changes (1,011.3 pg/ml) than in healthy controls (847.0 pg/ml) ($p < 0.05$). However, the level of this cytokine in SLE patients without skin symptoms was similar to the control group ($p > 0.05$). Similarly, the median concentration of bFGF was higher in SLE patients with skin involvement (3.2 pg/ml) than in the control group (1.2 pg/ml) ($p < 0.03$), or in patients without skin symptoms (0.9 pg/ml) ($p < 0.04$). bFGF levels higher than 3 pg/ml were found in 16 SLE patients with skin changes, 11 SLE patients without skin changes and 7 individuals from the control group. The levels of TGF-beta1 and VEGF were similar in patients with, or without, skin involvement and accordingly between those groups and healthy individuals ($p > 0.05$).

We found no statistically significant difference in the levels of cytokines, investigated in the patients with or without neurological symptoms. However, in the group of 37 patients with neurological symptoms 30 patients had only minor symptoms such as head-ache, poor concentration and mood swings, which are difficult to differentiate from other coexistant conditions. Only 7 patients had symptoms more specific for SLE, including seizures, stroke, depression, psychosis and disordered mentation.

We observed statistically significant differences in the levels of HGF and VEGF among patients with other clinical and laboratory SLE features. HGF serum levels were higher in patients with anaemia (Hct < 35%) (median 993.4 pg/ml) than in patients with Hct > 35% (median 838.8 pg/ml) ($p < 0.04$). The level of this cytokine was also higher in patients with serositis (median 1,243.2 pg/ml), than in patients without this symptom (median 852 pg/ml) ($p < 0.03$). The level of VEGF was higher in patients with immunoglobulin deposits at the dermal-epidermal junction (median 230.6 pg/ml) than in the patients without them (median 106.1 pg/ml) ($p < 0.02$). The serum concentration of VEGF was higher in

the patients with anti-ds DNA antibodies in the serum (median 230.6 pg/ml) than in patients in whom anti-ds DNA antibodies were not detected (median 118.1 pg/ml; $p < 0.03$) or in the control group (median 133.5 pg/ml; $p < 0.04$). The serum levels of HGF, bFGF and TGFbeta1 were similar in patients with and without anti-ds DNA antibodies.

The concentrations of HGF and VEGF were higher in patients with a high CRP level (> 4.7 mg/l) (median 1,075.2 and 327.3 respectively) than among patients with a low CRP level (< 4.7 mg/l) (848.7 pg/ml and 118.5 pg/ml, respectively) ($p < 0.04$ and $p < 0.02$ respectively). However, there was no difference in the levels of the investigated cytokines in the serum of the patients treated with steroids and those not treated with these agents. We found a positive correlation between HGF serum concentration and the SLE activity score ($r = 0.435$, $p < 0.001$) (Figure 1). A correlation between VEGF and SLE activity was also positive but its significance was lower than in the case of HGF ($r = 0.252$, $p = 0.05$). We found a significant correlation between the VEGF serum levels and the platelet count ($r = 0.272$, $p < 0.04$), as well as the TGF-beta1 concentration and platelet count ($r = 0.313$, $p < 0.02$) (Figure 2). In contrast, there was no correlation between HGF and bFGF concentrations and the platelet count. We found no positive correlation between HGF, bFGF, VEGF or TGFbeta1 serum levels and the concentrations of C3, C4, transaminase activity or erythrocyte sedimentation ($p > 0.05$).

We also examined the relationship between serum concentration of the cytokines. Significantly positive correlations are presented in Figure 3. We found significantly positive correlations between the levels of HGF and bFGF ($r = 0.268$, $p < 0.04$), TGF-beta1 ($r = 0.365$, $p < 0.005$) and VEGF ($r = 0.327$, $p < 0.02$). There was also a positive correlation between serum concentrations of VEGF and TGF-beta1 ($p = 0.543$, $p < 0.001$) (Figure 3). We found no correlation between the concentrations of bFGF and TGF-beta1 $p > 0.05$) or bFGF and VEGF ($rhô = 0.056$, $p > 0.05$). The only significant positive correlation in the control group was between the levels of HGF and VEGF ($rhô = 0.491$, $p = 0.02$).

DISCUSSION

In contrast to neoplastic diseases, the significance of angiogenesis, as well as angiogenic factors, in the pathogenesis of connective tissue diseases have not been very well investigated. The aim of our study was to evaluate the

concentration of four angiogenic cytokines in the serum of SLE patients and the correlation with the disease activity, selected clinical symptoms and laboratory parameters. We measured the serum levels of HGF, VEGF, bFGF and TGF-beta1, which are regarded as crucial factors in the angiogenesis process [5-16]. The reported levels of HGF, VEGF and TGFbeta1 were found in the serum of all 60 SLE examined patients and also in the serum of all the participants in the control group. Basic FGF however, was found in the serum of 70% of SLE patients and 65% of the healthy persons. Kadono *et al.* [10] found detectable amounts of this cytokine in 31 of the 74 patients diagnosed with SS, 7 of the 33 with dermatomyositis and in only 1 of the 12 SLE patients and accordingly in none of the 20 healthy persons. The possibility of more frequent detection of bFGF in our patients is probably connected with the higher sensitivity of the ELISA used by us (1 pg/ml) as compared with the 10 times lower sensitivity of the test used by Kadono *et al.* (10 pg/ml) [10].

VEGF was previously evaluated in the serum of patients with RA and connective tissue diseases [9, 16]. Kikuchi *et al.* measured the concentration of this angiogenic agent in 17 patients with SLE, 49 with PM/DM, 40 with SS, 11 with RA and 20 healthy persons [16]. The average VEGF concentration in the control group was 184 ± 62 pg/ml, similar to that found in our study (125.8 ± 60.7 pg/ml). The authors found a significantly higher VEGF concentration among patients with PM/DM and RA than in the control group. The serum level of VEGF in SLE patients was, however, similar to that in healthy volunteer group. A higher VEGF level among SLE patients in comparison to that of healthy persons was found by Harada *et al.* [9]. The results of our study show a higher serum concentration of this cytokine in patients with the active stage of the disease compared to inactive disease and the control group ($p < 0.05$ and $p < 0.04$, respectively).

To our knowledge there is no literature data concerning the HGF level in the serum of SLE patients. Our study showed, similarly to VEGF, a profoundly higher concentration of this cytokine in active SLE patients than in inactive SLE patients or in healthy persons ($p < 0.005$ and $p < 0.009$ respectively). We have further shown a positive correlation between the HGF and VEGF level and SLE activity (Figure 1). A similar correlation was previously found in RA patients [9]. It should be underlined, however, that the increased levels of HGF and VEGF in SLE patients with active disease, although statistically significant, may reflect a global deregulation of the cytokine network linked to multi-systemic and

inflammatory disorders including RA and other collagen diseases, rather than a specific feature of SLE.

It has been shown that angiogenesis is also involved in the skin lesions of SLE [23, 24]. The results of our research are in accordance with these observations. We have shown a higher concentration of HGF and bFGF among SLE patients with skin lesions in comparison to healthy persons and SLE patients without skin involvement (Table 3).

Our study shows higher levels of HGF and VEGF in SLE patients with an increased concentration of CRP, compared to the patient group with a normal level of this protein. Similar observations were made by Harada *et al.* [9] who revealed the positive correlation between VEGF level and CRP in patients with RA. The VEGF concentration also correlated with CRP in the group of patients with multiple myeloma [25].

We have shown a positive correlation between the concentrations of VEGF and TGF-beta1 and the blood platelet count, and no correlation with HGF and bFGF. A similar correlation between VEGF and the platelet count was found by Di Raimondo *et al.* in patients with multiple myeloma [25]. It seems that this correlation is connected with VEGF accumulation in platelets and megacaryocytes [20]. Similarly to our findings, but in a group of multiple myeloma patients, no correlation was found between the platelet count and bFGF, HGF serum levels [25].

The statistical analysis of data showed a positive correlation between HGF serum levels and the remaining three angiogenic agents (VEGF, bFGF and TGF-beta1) and also between the serum concentrations of VEGF and TGFbeta1 (Figure 3). Similar relationships were found in multiple myeloma patients [25]. This may indicate a similarity in the regulatory processes during the production of these cytokines. The fact that TGF-beta1 is a strong inducer of VEGF production may argue for such an interpretation [27]. Other cytokines may also influence the production of angiogenic agents. IL-6, the serum concentration of which also correlates with SLE activity, was proved to be a stimulant of VEGF excretion [20, 28]. On the other hand, the lack of correlation between the level of other angiogenic cytokines *i.e.* TGF-beta1 and bFGF or VEGF and bFGF, may be related to the production of these cytokines by different cell types [25].

It should be emphasized that the process of angiogenesis results from a balance between angiogenic and antiangiogenic cytokines [1, 29]. The switch to the angiogenic phenotype involves a change in the local equilibrium between positive and negative regulators of the growth of microvessels [1, 7]. Several systemic diseases may be associated with inappropriate activation of the chemokine network. Some chemokines such as MCP-1/CCL-2 or the ELR^+ family of CXC chemokines may stimulate angiogenesis, but other act antagonisticaly to this process (IP-10/CXCL-10 SLC/CCL-21) [30-32]. Moreover, some interleukins such as IL-4, IL-12 and IL-18 also inhibit angiogenis [32-35].

The results of our study are in accordance with the suggestion that angiogenesis and certain angiogenic factors may be important in the pathogenesis of SLE [23, 24, 36]. This is a basis for further studies of the role of anti-angiogenic drugs in the treatment of such diseases. Preliminary observations show that drugs such as thalidomide, can be of benefit in SLE, especially in those cases where conventional therapy is ineffective [37, 38]. Several other antiangiogenic agents are currently undergoing clinical trials [6, 39].

CONCLUSION

In conclusion, it seems that angiogenic cytokines, such as HGF and VEGF play an important role in the active phase of SLE. Their serum levels could serve as a marker of SLE activity, but further studies are needed. Although many questions remain to be answered, we can speculate that the angiogenesis process is involved in the pathogenesis of SLE.

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Figures

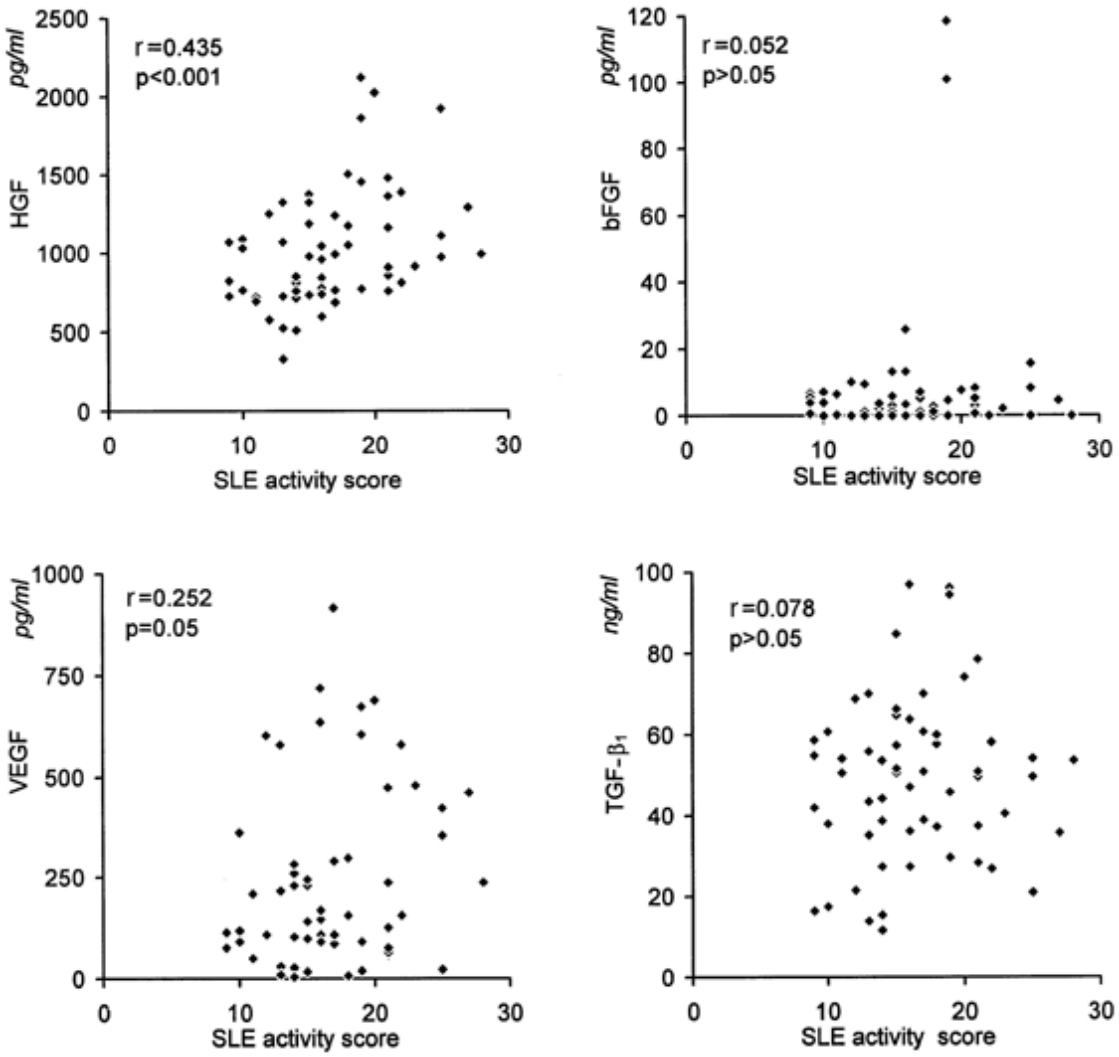


Figure 1
Correlation between serum levels of HGF, bFGF, VEGF, TGF-beta1 and the SLE activity.

There is a positive correlation between HGF and VEGF serum concentrations and the SLE activity score according to the Systemic Lupus Activity Measure (SLAM).

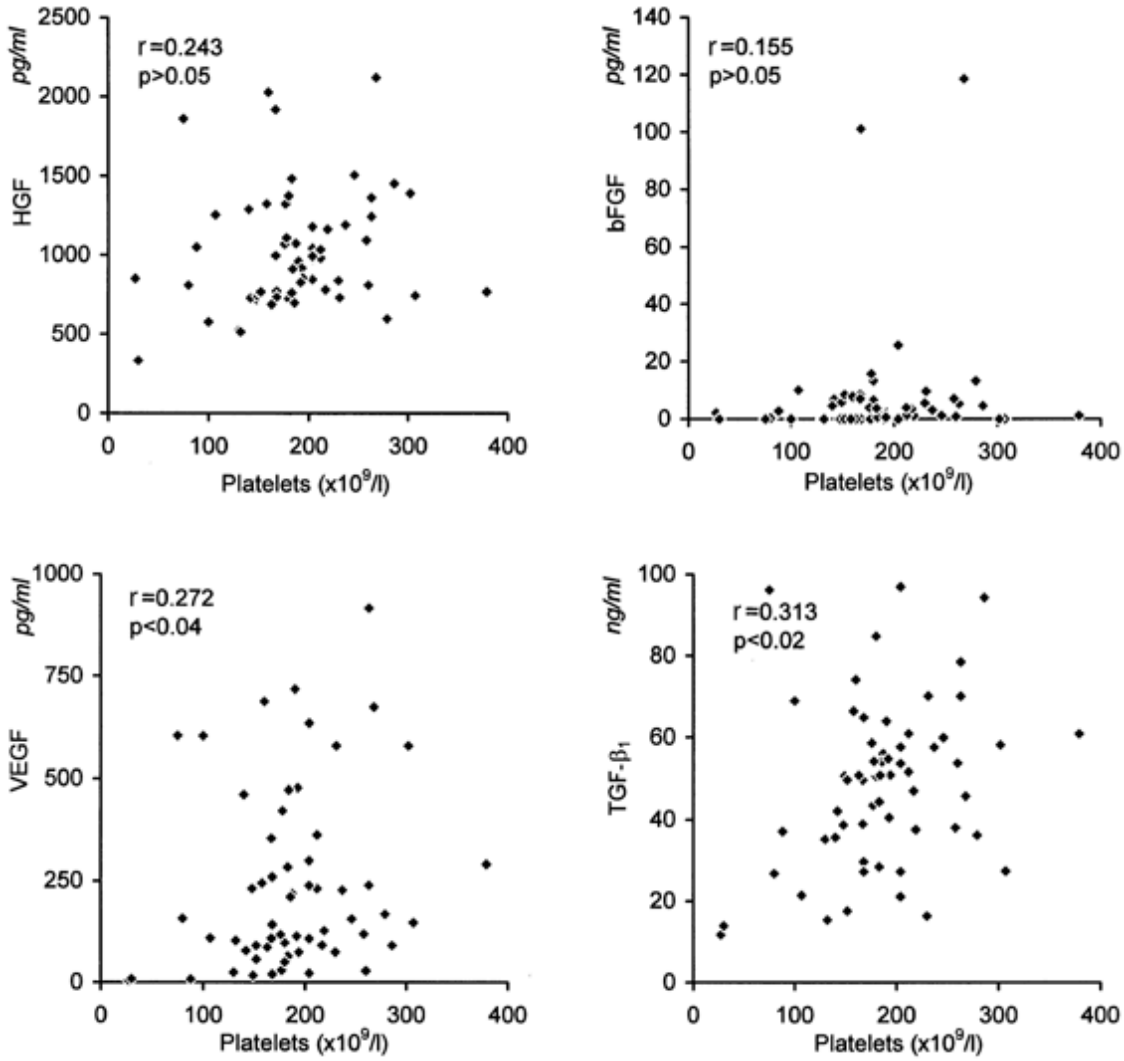


Figure 2

Correlation between serum levels of HGF, bFGF, VEGF, TGF-beta1 and platelets number.

A significant correlation between the VEGF and TGF-beta1 serum levels and the platelet count was found.

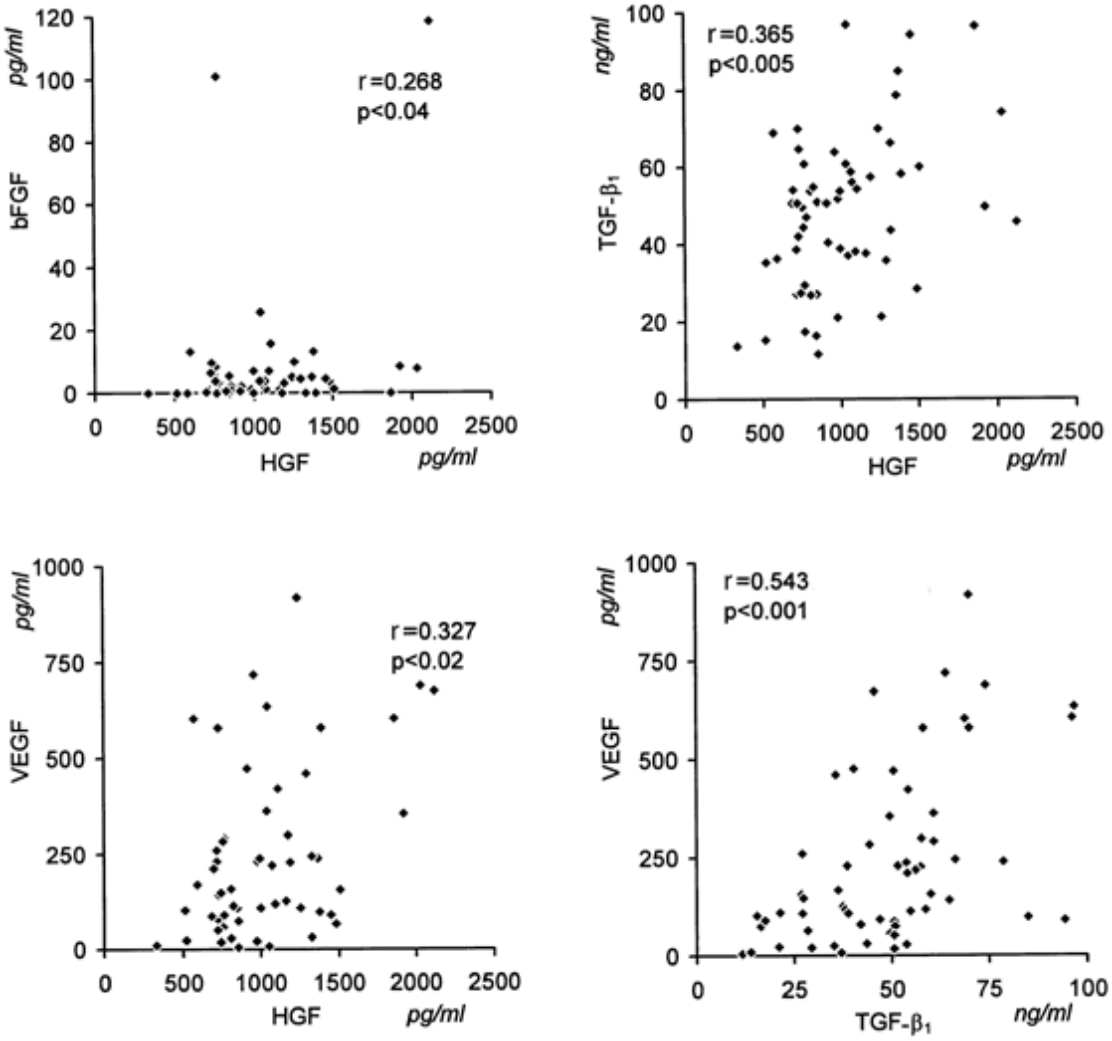


Figure 3

The relationship between serum concentration of selected angiogenic cytokines HGF, bFGF, VEGF, TGF-beta1 are presented.

Significant correlations between the levels of HGF and bFGF, TGF-beta1 and VEGF were found. There was also a positive correlation between serum concentrations of VEGF and TGF-beta1.

Table 1
Clinical and laboratory characteristics of patients with SLE

Symptoms	Number of patients	%
Total	60	100.0
Age (mean years, range)	40 (17-76)	–
Sex (male/female)	5/55	8.3/91.7
Active/inactive	32/28	53.3/46.7
Fever	14	23.3
Arthritis	55	91.7
Skin symptoms		
Reticuloendothelial	30	50.0
system involvement	36	60.0
Cardiovascular symptoms	11	18.3
Renal disorder (creatinine >1.3 mg/dl)	4	6.6
Serositis	9	15.0
Neurological symptoms	37	61.7
Antinuclear antibodies		
Anti-ds DNA antibodies	17	28.3
Immunoglobulin deposits	50	83.3
at the dermal-epidermal junction	35	58.3
Anaemia (Hct < 35%)	21	35
Lymphopenia (< 1,500 × 10^9/L)	39	65.0
Leukopenia (WBC < 3.5 × 10^9/L)	19	31.7
Thrombocytopenia		
(platelets < 150 × 10^9/L)	13	21.7
Raised ESR (> 25 mm/h)	24	82.8
C reactive protein > 4.7 mg/l	16	26.7
Treatment with steroids during the study	14	23.3
Treatment with cytotoxic agents during the study	5	8.3

Table 2
Serum levels of HGF, bFGF, VEGF and TGF-beta1 in patients with SLE and the healthy control group (values of VEGF, bFGF and HGF are in pg/ml, and TGF-beta1 in ng/ml)

Cytokines	All SLE patients n = 60 (a)	Active SLE n= 32 (b)	Inactive SLE n = 28 (c)	Control group n = 20 (d)	Statistically significant comparison
HGF					
Mean ± SD	1,014.3 ± 371.0	1,142.4 ± 405.0	688.0 ± 266.2	845.7 ± 266.8	(b)-(c)-(d) $p < 0.005$
Median	939.1	1,019.5	787.8	847.0	(b)-(c) $p < 0.005$
Range	(332.2-2,120.6)	(595.4-2,120.6)	(332.2-1,374.5)	(189.0-1,389.9)	(b)-(d) $p < 0.009$
bFGF					
Mean ± SD	7.2 ± 19.9	10.7 ± 26.7	3.1 ± 3.7	1.9 ± 2.3	all groups $p > 0.05$
Median	1.65	2.45	1.2	1.2	
Range	(0-118.5)	(0-118.5)	(0-43.5)	(0-7.8)	
VEGF					
Mean ± SD	237.2 ± 219.9	298.8 ± 251.5	116.8 ± 152.8	125.8 ± 60.7	(b)-(c)-(d) $p < 0.05$
Median	151.8	203.5	116.1	133.5	(b)-(c) $p < 0.05$
Range	(5.4-916.7)	(8.1-916.7)	(5.4-603.4)	(21-217.4)	(b)-(d) $p < 0.04$
TGF-beta1					
Mean ± SD	48.6 ± 20.0	51.5 ± 20.3	45.3 ± 19.5	48.3 ± 15.8	all groups $p > 0.05$
Median	50.5	50.2	50.5	52.7	
Range	(11.7-96.9)	(21.1-96.9)	(11.7-84.8)	(11.7-70.6)	

Table 3
Serum levels of HGF, bFGF, VEGF and TGF-beta1 in patients with SLE, with and without skin symptoms (values of HGF, bFGF and VEGF are in pg/ml, TGF-beta1 in ng/ml)

Cytokines	Skin symptoms present n = 30 (a)	No skin symptoms n = 30 (b)	Control group n = 20 (c)	Statistically significant comparison
HGF				
Mean ± SD	1,080 ± 380.4	948.1 ± 355.4	845.7 ± 266.8	(a)-(b)-(c) $p = 0.05$
Median	1,011.3	884.6	847.0	(a)-(c) $p < 0.05$
Range	(595.4-2,028.4)	(332.2-2,120.6)	(189.0-1,389.9)	
bFGF				
Mean ± SD	8.2 ± 18.5	6.2 ± 21.5	1.9 ± 2.3	(a)-(b)-(c) $p < 0.04$
Median	3.2	0.9	1.2	(a)-(b) $p < 0.04$
Range	(0-101.1)	(0-118.5)	(0-7.8)	(a)-(c) $p < 0.03$
VEGF				
Mean ± SD	242.4 ± 196.6	232.0 ± 244.4	125.8 ± 60.7	all groups $p > 0.05$
Median	189.4	123.1	133.5	
Range	(8.1-687.8)	(8.1-916.7)	(21-217.4)	
TGF-beta1				
Mean ± SD	52.8 ± 20.7	44.4 ± 18.7	48.5 ± 15.8	all groups $p > 0.05$
Median	51.2	45.1	52.7	
Range	(17.5-96.9)	(11.7-84.8)	(11.7-70.6)	

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Plasmodium berghei, protection, rmGM-CSF, met-enkephalin.

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microsatellites, interleukin-10 promoter, multiplex-PCR, Caucasian, African.

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