Vascular endothelial growth factor in systemic lupus erythematosus in correlations with disease activity and nailfold capillaroscopic changes

Sherin M.H. Hamza, Nermeen S. Khalil, Rasha M. Hamoda, Marwa A. El-Asfahani

Department of Internal Medicine and Rheumatology, Ain Shams University, Cairo, Egypt

Correspondence to Nermeen S. Khalil, PhD, MD, Lecturer of Internal Medicine; Department of Internal Medicine and Rheumatology, Ain Shams University, Cairo, Egypt.
Tel: +20 122 374 4672;
e-mail: dr.nermeen81@gmail.com

Received: 16 February 2019
Revised: 4 March 2019
Accepted: 10 March 2019
Published: 18 August 2020

The Egyptian Journal of Internal Medicine
2019, 31:943–950

Background
Angiogenesis plays a role in the pathogenesis of systemic lupus erythematosus (SLE). Both serum vascular endothelial growth factor (VEGF) and capillaroscopic abnormalities may reflect intensity of microcirculatory changes in the course of SLE.
Aims
To quantify serum VEGF level and its correlation with microvascular changes, assessed by nailfold capillaroscopy (NFC), and possible relationship with SLE activity.
Patients and methods
A total of 90 patients with SLE were subjected to detailed medical history and clinical examination and assessment of disease activity using the SLE Disease Activity Index score and organ damage using Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index. Laboratory investigations were done including autoantibodies [anti-nuclear antibody, anti-DNA, anti-cardiolipin (immunoglobulin G and immunoglobulin M), and lupus anticoagulant]. VEGF serum level was measured using enzyme-linked immunosorbent assay. NFC examination was done for recognition of NFC abnormalities.
Results
Serum VEGF level was elevated in the entire study group (mean of 831±572 ng/l), with a statistically highly significant correlation with Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index and SLE Disease Activity Index score of disease activity (r=0.349, P=0.001, and r=0.897, $P<0.001$, respectively), together with a significant positive correlation with the presence of nephritis (P=0.002), positive anti-double-stranded DNA ($P\leq0.001$), and consumed C3 and C4 ($P\leq0.001$), which are laboratory markers indicating lupus activity. Moreover, a higher serum VEGF level was associated with severe NFC changes with a statistically highly significant positive correlation with the capillary width (r=0.561, $P<0.001$), capillary length (r=0.411, $P<0.001$), and mean capillary density (r=0.308, P=0.003).
Conclusion
Increased serum VEGF level and progression of NFC score had been directly related to lupus activity and internal organ involvement, especially nephritis.

Keywords:
damage index, disease activity, nailfold capillaroscopy, systemic lupus erythematosus, vascular endothelial growth factor

Egypt J Intern Med 31:943–950

1110-7782

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune connective tissue disorder. Angiogenesis plays a significant role in the pathophysiology of SLE through a controlled sequence of endothelial cell growth, extracellular matrix remodeling, endothelial cell migration, and new capillary formation [1].

Both serum vascular endothelial growth factor (VEGF), a key regulator of angiogenesis, and capillaroscopic abnormalities may reflect intensity of microcirculatory changes in the course of SLE with both diagnostic and prognostic purpose [2].

The aim of this study is quantification of serum VEGF level and its correlation with microvascular changes, assessed by nailfold capillaroscopy (NFC), and possible relationship with SLE activity.

Patients and methods

This is a cross-sectional study that included 90 patients with SLE who fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE [3]. Our patients were recruited randomly from rheumatology outpatient clinic and inpatient department at Ain Shams University Hospitals. Patients with diabetes mellitus, hypertension, associated or overlap autoimmune CT diseases, Raynaud's phenomenon, and other peripheral vascular diseases were excluded. Approval was taken from Ain Shams University Medical and Ethical Committee and conforms to the provisions of the Declaration of Helsinki in 1995. Verbal consent was taken from patients after informing them about participation in the study.

All patients were subjected to the following: detailed medical history and full clinical examination including rheumatological examination with assessment of the SLE Disease Activity Index [4] and the Systemic Lupus International Collaborating Clinics damage index [5]. Laboratory investigations were done including complete blood count, erythrocyte sedimentation rate (ESR) in the first hour, C-reactive protein, liver enzymes, serum blood urea nitrogen, creatinine, complete urine analysis, protein/creatinine ratio, and total 24-h urinary protein. Serological biomarkers, including anti-nuclear antibody, anti-double-stranded DNA (anti-dsDNA) by indirect immunofluorescence, anti-cardiolipin blood test for immunoglobulin G and immunoglobulin M, lupus anticoagulant using enzyme-linked immunosorbent assay, and also complement 3 (C3) and complement 4 (C4), were assessed.

The serum concentrations of VEGF were assessed by an enzyme-linked immunosorbent assay kit. Assays were carried out according to the manufacturers' instructions. Normal serum level of VEGF is less than 22.5 ng/l [6].

NFC was performed using a videocapillaroscope (Videocap 3.0; DS Medica) by the same examiner and according to the standardized methods [7]. The following NFC parameters were evaluated: (a) distribution (normally is parallel rows); (b) shape of capillaries is described as normal (stereotype hairpin shape, without bending or crossing of limbs), tortuous (both the limbs bend but do not cross), or crossing (the limbs cross once or twice). Capillaries were documented as 'normal hairpin' shape, whereas all other shapes were documented as 'abnormal' shapes; (c) width is the distance between two limbs of the capillary loop. Vascular loop's estimated normal width is less than 20 μm, dilated 20–50 μm, or giant more than 50 μm; (d) length was determined by measuring the projection of the capillary visible part. Loops longer than 300 μm were interpreted as elongated capillaries; (e) mean capillary density equals the number of capillaries at the nailfold, per linear mm and per field examined. Avascularity was defined as the absence of more than two successive capillaries in one examined field or as a desert-like appearance; (f) hemorrhages are extravasations of red blood cells into the perivascular tissue as pearl necklaces of extravasates or as extra-capillary brown aggregations of erythrocytes; and (g) visibility of subpapillary plexus [7].

NFC scoring was estimated, which is a semiquantitative scoring that rates the capillaroscopic changes from zero to three or in the wordings normal/minor/major/severe pattern. (a) Score 0 (normal) was defined as no changes in density, dimension, morphology, or hemorrhages. (b) Score 1 (minor) was defined as mild changes [normal density (6–8 capillaries/linear mm), <10% longer capillaries, <50% morphological changes, and absence of hemorrhages]. (c) Score 2 (major) was defined as moderate changes (normal or decreased density >10% of capillaries that were elongated, >50% morphological changes, and presence of hemorrhages). (d) Score 3 (severe) was defined as severe changes (<6 capillaries/linear mm, >10% of capillaries that were elongated, >75% morphological changes, and presence of hemorrhages) [8].

Statistical analysis

Data were collected, revised, coded, tabulated, and statistically analyzed using Statistical Package for Social Science (IBM SPSS) program, version 23. Unpaired Student t test and c^2 test were used to compare quantitative and qualitative variables, respectively. Analysis of variance test was used for comparison among different times in the same group. Linear correlation coefficient was used for detection of correlation between two quantitative variables in one group. P value was considered significant at the level of less than 0.05, and P value less than 0.01 was highly significant.

Results

Of our 90 patients with SLE, 80 (89%) were females and 10 (11%) were males. All clinical manifestations, disease activity indices, organ damage score, drugs received, and laboratory data are presented in Table 1. Serum VEGF level was elevated in the

Table 1 All descriptive data of our 90 patients with systemic lupus erythematosus (demographic, clinical, laboratory data including vascular endothelial growth factor measurement, and drug intake)

Mean±SD (range) or *n* (%)	SLE patients (*N*=90)	
Age (years)	15–47	27±8
Age of onset of SLE (years)	14–44	22±6
Disease duration (years)	1–22	5±5
BMI (kg/m^2)	20–31	22±3
Sex		
Male	10	11
Female	80	89
Smokers	10	11
Malar rash	65	72
Photosensitivity	65	72
Oral ulcers	56	62
Nonscarring alopecia	67	74
Arthritis or arthralgia	54	60
Morning stiffness	8	9
Renal manifestations	57	63
Neuropsychiatric manifestations	30	33
Cardiac manifestations	19	21
Pulmonary manifestations	36	40
Hematologic manifestations	38	42
GIT manifestations	69	77
Serositis	23	25
Livedo reticularis	0	0
Thromboembolic manifestations	9	10
Recurrent abortion	11	12
Drug intake		
Oral steroid dose (mg)	7.5–40	21±7
Duration of steroid intake (years)	1–22	5±5
Oral steroid intake	90	100
Hydroxychloroquine	90	100
i.v. pulse steroid	57	63
i.v. cyclophosphamide	36	40
Azathioprine	70	78
Mycophenolate mofetil	21	23
Cyclosporine	2	2
Antiplatelets (low dose aspirin)	48	53
SLEDAI		
Mild (<6)	14	15
Moderate (6–12)	49	54
Severe (>12)	27	30
Range/mean±SD	4–26	11±6
SLICC/ACR damage index	1–3	2±0.6
WBCs (10^3 cells/ml)	1.9–18	7±4
Lymphocytes (10^3 cells/ml)	0.3–4	2±0.7
Hb (g/dl)	7–15	11±2
PLT (10^3 cells/ml)	50–700	268±114
ESR (mm/h)	3–135	62±43
CRP (mg/l)	6–96	18±24
AST (U/l)	7–55	24±12
ALT (U/l)	4–65	19±15
BUN (mg/dl)	5–69	15±12
Serum creatinine (mg/dl)	0.4–3.4	0.8±0.5
P/C ratio	0.05–3.5	0.8±1
24 h urinary protein mg/day	50–5661	734±1209
Complete urine analysis		
Proteinuria	60	67
Hematuria	14	15
RBCs cast	11	12
Pus cells	37	41
ANA +ve	90	100
Anti-dsDNA +ve	46	51
↓C3 (mg/dl)	27	30
↓C4 (mg/dl)	27	30
ACL IgG/ IgM +ve	0	0
LAC +ve	2	2
VEGF (ng/l)	180–2700	831±572

(*Continued*)

ACL, anti-cardiolipin; ALT, alanine transaminase; ANA, anti-nuclear antibody; AST, aspartate transaminase; BUN, blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GIT, gastrointestinal tract; Hb, hemoglobin; IgG, immunoglobulin G; IgM, immunoglobulin M; i.v., intravenous; LAC, lupus anticoagulant; P/C, protein/creatinine ratio; PLT, platelet; RBC, red blood cell; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC/AACR, Systemic Lupus International Collaborating Clinics/American College of Rheumatology; VEGF, vascular endothelial growth factor; WBC, white blood cell.

entire study group, which ranged from 180 to 2700 ng/l, with a mean of 831±572 ng/l. NFC showed multiple pathological changes in the capillary vessels of our studied group, as shown in Table 2 and Figs 1–4.

A comparative study using *t* test, revealed a statistically highly significant increase in serum VEGF level in patients with recurrent abortions, as well as renal and hematologic manifestations, with *P* values of less than 0.001, 0.002, and less than 0.001, respectively (Fig. 5). Moreover, the mean serum level of VEGF was highly significantly elevated in patients with history of intake of pulse steroids, cyclophosphamide, and mycophenolate mofetil, with *P* value of less than 0.001, 0.001, and less than 0.001, respectively, Regarding various laboratory data, we found a statistically highly significant increase in serum VEGF levels among patients who had positive anti-dsDNA ($P \leq 0.001$) and consumed C3 and C4 ($P \leq 0.001$). Moreover, there was a statistically highly significant increase in mean serum VEGF levels in patients having red blood cell cast ($P \leq 0.001$) and puria ($P \leq 0.001$) in simple urine analysis, with only significant increase regarding proteinuria ($P = 0.015$) (Fig. 5).

Using analysis of variance and *t* tests, the serum VEGF level was highly significantly elevated regarding NFC findings among our patients, including the shape of the capillaries, especially the branching one, presence of avascular area, and presence of capillary hemorrhage, and also significantly elevated with the disarrangement of capillaries, with *P* values of 0.004,less than 0.001,

Table 2 Nailfold capillaroscopy findings among the studied 90 patients with systemic lupus erythematosus

NFC findings		
	Range	Mean±SD
Capillary width (μm)	15–60	35±11
Capillary length (μm)	77–350	165±73
Mean capillary density (no/mm)	6–90	12±12
	SLE patients (*N*=90) [*n* (%)]	
Shape		
Hair pin	34 (38)	
Tortuous	45 (50)	
Branching	5 (5.5)	
Tortuous and branching	6 (7)	
Distribution		
Parallel row	56 (62)	
Disarranged	34 (38)	
Avascular area	4 (4)	
Capillary hemorrhage	38 (42)	
Subpapillary plexus	25 (28)	
NFC severity score		
0	17 (19)	
1	35 (39)	
2	22 (24)	
3	16 (18)	

NFC, nailfold capillaroscopy; SLE, systemic lupus erythematosus.

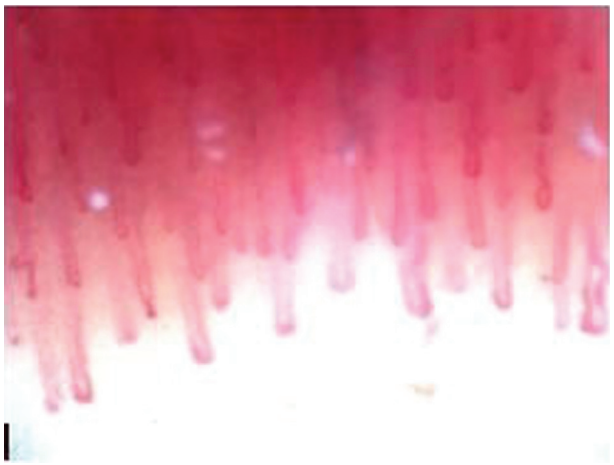
less than 0.001, and 0.002, respectively. Regarding the correlations between mean serum levels of VEGF and different demographic, clinical, and laboratory data and drug intake, results are shown in Table 3 and Figs 6–8.

Discussion

VEGF is a key regulator of angiogenesis that stimulates endothelial cell proliferation, differentiation, and survival. Moreover, it mediates dependent vasodilatation, microvascular hyperpermeability, and interstitial matrix remodeling. Elevated serum levels are found in chronic inflammatory rheumatologic diseases, including SLE [4]. In the current study, our patients with SLE had higher serum level of VEGF than the normal range. This finding was in agreement with others [9–11] who found significantly elevated VEGF levels in patients with SLE than controls, and this supports the postulation that serum VEGF may play an important role in the pathogenesis of SLE. This finding was also supported by the results of a study done by Avihingsanon *et al.* [12], who reported a decrease in serum VEGF levels in response to lupus treatment.

Kuryliszyn-Moskal *et al.* [9] found that serum VEGF level was high in patients with organ involvement, although no significant differences between the SLE groups with and without systemic manifestations were found. Our results revealed an elevation of serum levels of VEGF in patients with nephritis with significant positive correlation with protein/creatinine ratio, 24-h urine protein, and serum creatinine, indicating that VEGF may participate in the pathogenesis of lupus nephritis. This was in consistence with others [11,13,14]. VEGF loss is combined with the occurrence of glomerulosclerosis and tubulointerstitial fibrosis in the remnant kidney, and this makes VEGF an important diagnostic marker of active nephritis [14]. Moreover, Navarro *et al.* [15] reported that patients with renal failure had significant high plasma levels and overexpression of VEGF in renal tissue. Moreover, the study by Heshmat and El-Kerdany [16] stated that serum VEGF appeared to mediate glomerular endothelial repair, promoting healing from glomerular injury, and it has been recommended as an emerging therapeutic target to glomerular diseases characterized by endothelial damage, such as various glomerulonephritis and renal transplant rejection.

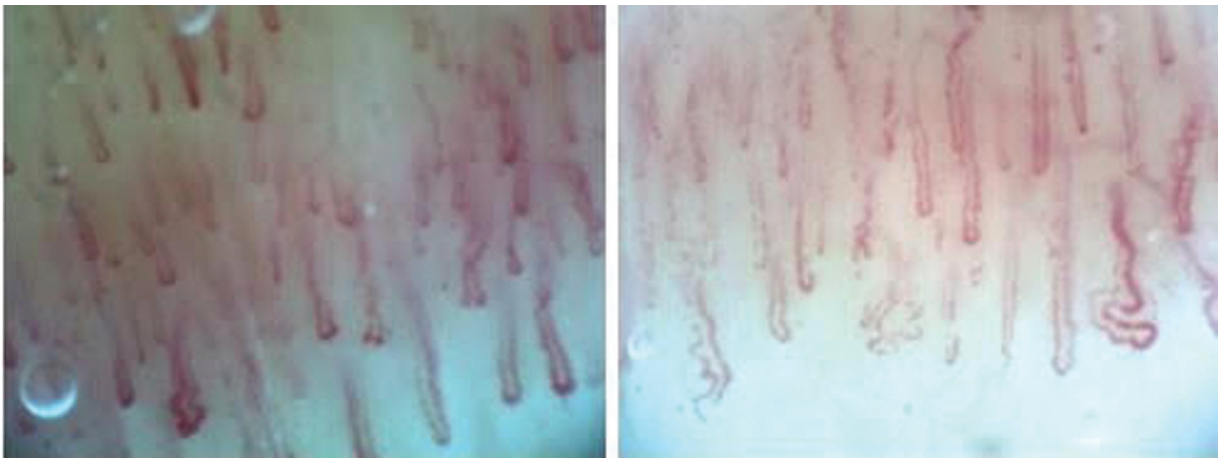
Figure 1



NFC score 0 showing hairpin-shape capillaries, no changes in density and dimension, and no hemorrhages. NFC, nailfold capillaroscopy.

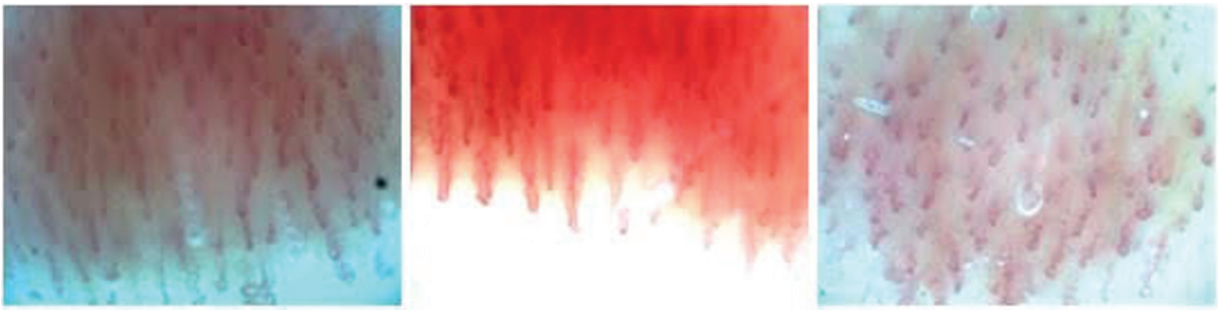
The present study also documented a statistically highly significant positive correlation between serum VEGF and disease activity, as assessed by SLE Disease Activity Index score, suggesting that it may be a good evaluation marker. A similar association was also reported by other studies [4,7,9,10,17]. On the contrary, a study done by Zhou *et al.* [14] found no relation between serum VEGF level and active disease, which may be supported by the fact that the angiopathy in active lupus is somewhat declined in response to immunosuppressive treatment. A significant positive correlation between serum VEGF and serological biomarkers of lupus activity, including presence of positive anti-dsDNA and consumed of C3 and C4, was reported by Iman *et al.* [1], who stated that a high

Figure 2



NFC score 1 showing mild changes of the capillaries [normal density, <10% longer capillaries, <50% morphological changes (tortuous and branching), and absence of hemorrhages]. NFC, nailfold capillaroscopy.

Figure 3



NFC score 2 showing moderate changes of the capillaries [decreased density >10% of elongated capillaries, >50% morphological changes (tortuous), and areas of hemorrhages]. NFC, nailfold capillaroscopy.

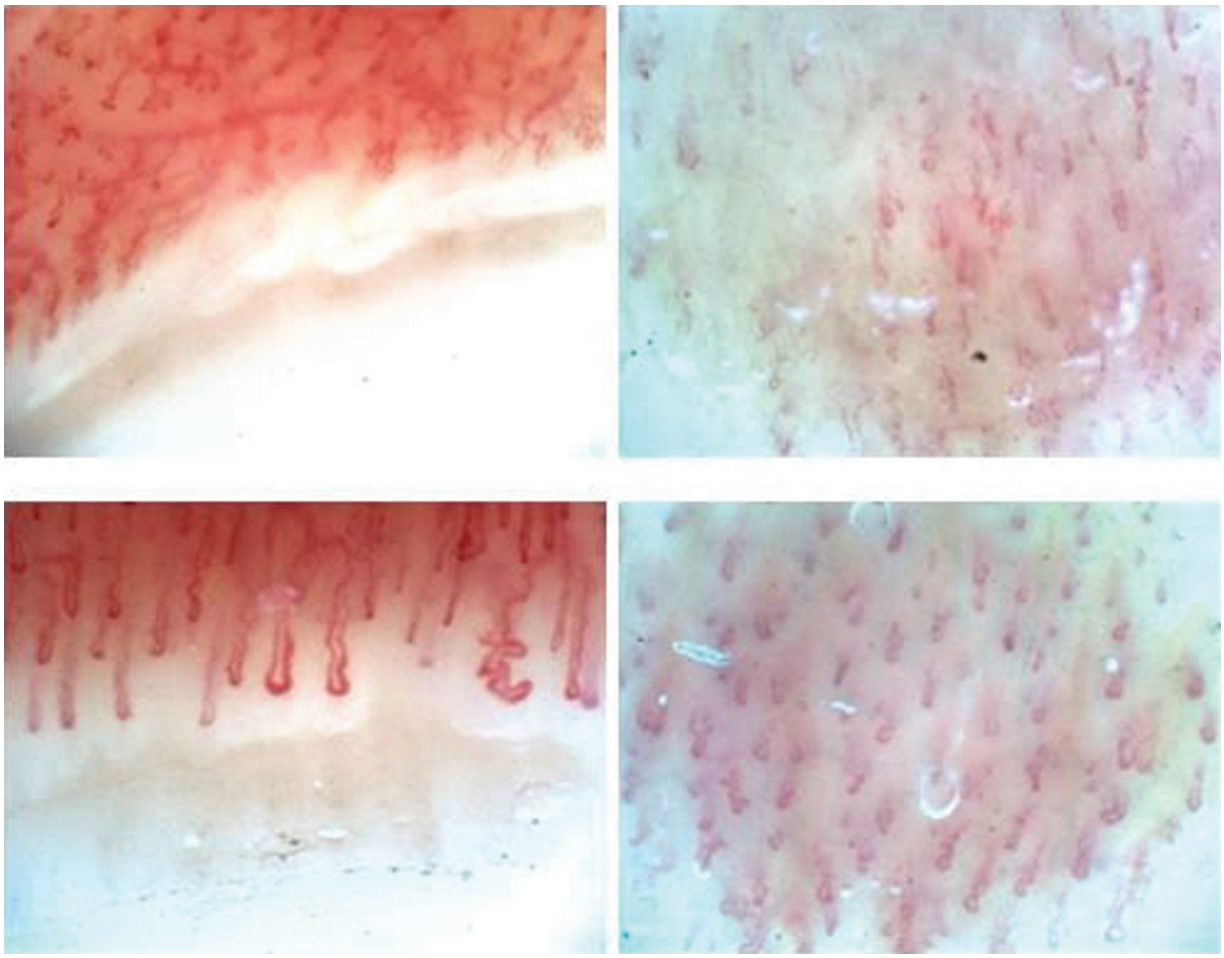
angiogenic activity was observed in patients with lupus with positive anti-dsDNA antibodies, which were in agreement with our results. Our findings were also in accordance with the findings of other studies [12,13]. However, a study done by Kuryliszyn-Moskal *et al.* [9] found no correlation between serum VEGF and positive anti-dsDNA, despite higher levels of anti-dsDNA antibodies in the group with systemic complications compared with those without. Moreover, the results of Zhou *et al.* [14] and Bărbulescu *et al.* [7] were consistent with ours, as they reported a direct positive correlation between serum VEGF and acute-phase reactants (ESR and C-reactive protein), indicating active inflammation. However, in a study done by Iman *et al.*, [1], there was no correlation between serum VEGF level and ESR level.

Regarding other laboratory data, our results showed a highly significant negative correlation between VEGF serum levels and hemoglobin levels ($P<0.001$), which was similar to other studies [14,18]. This can be related to the fact that the nutritional conditions of the patients gradually deteriorate during disease activity, which is associated with increased serum VEGF levels. This result was in contrast to that reported by Iman *et al.* [1].

Our data reported that serum VEGF level was significantly highly associated with the steroid dose, duration of steroid intake, and also with the history of pulse steroid intake. This was in agreement with those of Iman *et al.* [1], who stated that steroids are well-known regulators of VEGF and have a suggested mediatory function in the secretion of VEGF. Moreover, we reported a significant association between the mean serum VEGF level and immunosuppressive therapies including pulse cyclophosphamide and mycophenolate mofetil. This was in contrast with previous studies [1,9] who found that the serum levels of VEGF were the same in lupus cases with and without immunosuppressive treatment.

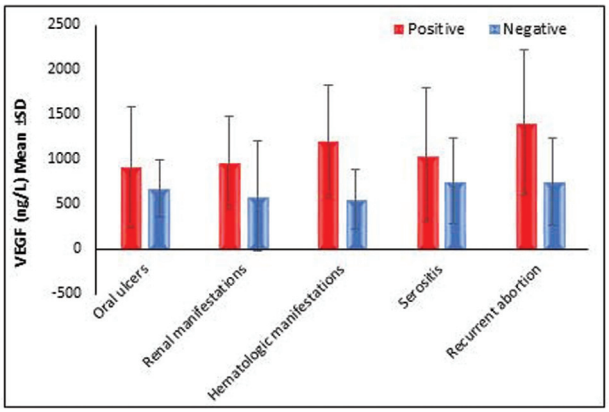
We studied NFC patterns in patients with lupus for better evaluation of microcirculation *in vivo* and

Figure 4



NFC score 3 showing severe changes of the capillaries (decreased density, >10% elongated capillaries, >75% morphological changes, and areas of hemorrhages). NFC, NFC, nailfold capillaroscopy.

Figure 5



Comparison between mean serum VEGF levels among studied patients with SLE regarding the presence and absence of some clinical manifestations. SLE, systemic lupus erythematosus; VEGF, vascular endothelial growth factor.

assessment of the peripheral angiopathic changes of this autoimmune condition and possible correlation with serum VEGF. Our data showed that a variety of bizarre major capillary abnormalities were frequently observed in our patients, including increased tortuosity, variability in loop length and width, capillary hemorrhages, and subpapillary plexus; however, no specific pattern was noted. These data match the results of previous studies [9,10].

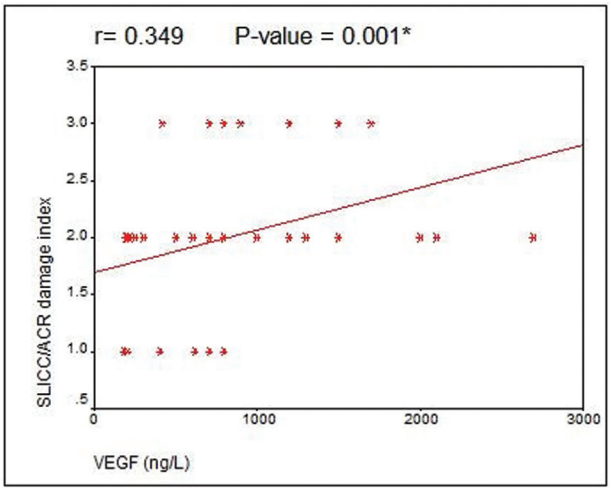
Our results revealed high significant association between serum VEGF level and capillaroscopic findings, including capillary width and length and mean capillary density. This association proves that VEGF reflects the microcirculatory changes in patients with SLE, as reported by other studies [7,10,16]. Furthermore, we observed a significant positive correlation between VEGF serum level and NFC severity score among our patients. Higher VEGF serum levels were reported in cases with severe capillaroscopic changes than those with mild changes; these findings were similarly reported by other studies [7,9,10]. This may be explained by that the vascular conditions occurring in SLE, which include inflammation, vessel occlusion, or thickening of the vascular wall, might be a potent stimulus for

Table 3 Correlation between serum vascular endothelial growth factor level and various demographic, clinical, laboratory data and nailfold capillaroscopy findings

Data	VEGF (ng/l)		Significance
	r	*P* value	
Age (years)	−0.341	0.001	HS
Age of onset of SLE (years)	−0.247	0.019	S
Disease duration (years)	−0.250	0.018	S
BMI (kg/m^2)	−0.067	0.532	NS
Steroid intake			
Oral steroid dose (mg)	0.454	<0.001	HS
Duration (years)	−0.227	0.032	S
SLICC/ACR damage index	0.349	0.001	HS
SLEDAI score	0.897	<0.001	HS
WBCs (10^3 cells/ml)	−0.169	0.112	NS
Neutrophils (10^3 cells/ml)	−0.257	0.014	S
Lymphocytes (10^3 cells/ml)	−0.038	0.720	NS
Hb (g/dl)	−0.555	<0.001	HS
PLT (10^3 cells/ml)	0.011	0.921	NS
ESR (mm/h)	0.486	<0.001	HS
CRP (mg/l)	0.264	0.012	S
AST (U/l)	0.247	0.019	S
ALT (U/l)	0.217	0.040	S
BUN (mg/dl)	0.196	0.069	NS
Serum creatinine (mg/dl)	0.219	0.038	S
P/C ratio	0.417	<0.001	HS
24 h urinary protein mg/day	0.389	<0.001	HS
NFC findings			
Capillary width (μm)	0.561	<0.001	HS
Capillary length (μm)	0.411	<0.001	HS
Mean capillary density (no/mm)	0.308	0.003	HS

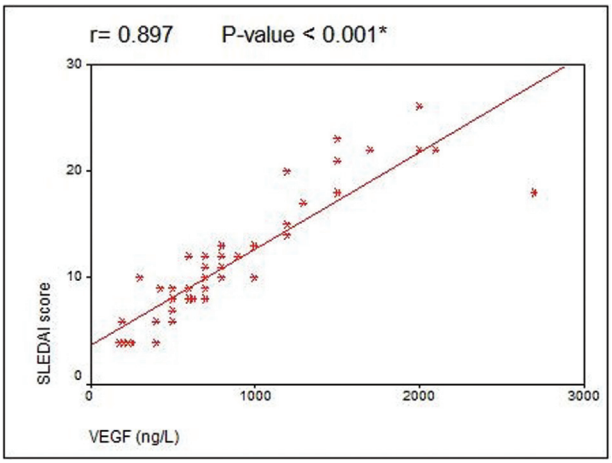
ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HB, hemoglobin; HS, highly significant; NFC, nailfold capillaroscopy; NS, nonsignificant; P/C, protein/creatinine ratio; PLT, platelet; S, significant; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC/AACR, Systemic Lupus International Collaborating Clinics/American College of Rheumatology; VEGF, vascular endothelial growth factor; WBC, white blood cell.

Figure 6



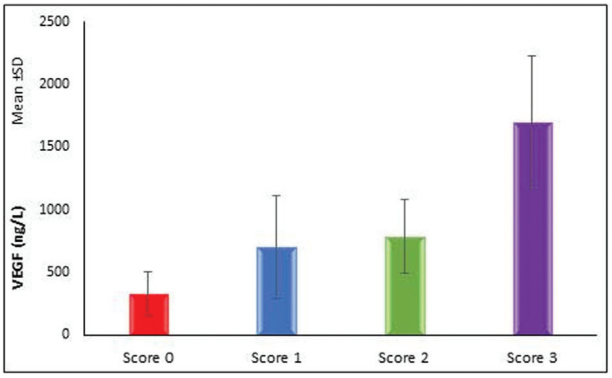
Correlation between mean serum VEGF levels and SLICC/ACR damage index among our patients with SLE. SLE, systemic lupus erythematosus; SLICC/ACR, Systemic Lupus International Collaborating Clinics/American College of Rheumatology; VEGF, vascular endothelial growth factor.

Figure 7



Correlation between mean serum VEGF levels and SLEDAI score among our patients with SLE. SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; VEGF, vascular endothelial growth factor.

Figure 8



Relation between NFC stages and mean serum VEGF level among our patients with SLE. NFC, NFC, nailfold capillaroscopy; SLE, systemic lupus erythematosus; VEGF, vascular endothelial growth factor.

angiogenic factor production, which shows a proportional increase with the vascular changes [10].

In conclusion, increased serum VEGF level (a key mediator of endothelial dysfunction and modulator of neovascularization) and progression of NFC score had been directly related to disease activity and systemic organ affection, especially lupus nephritis. This proves that serum VEGF reflects the microcirculatory changes in patients with SLE, which could be evaluated by nail capillaroscopy. Owing to the major involvement of endothelial dysfunction in the process of microvascular remodeling secondary to systemic inflammation in SLE and its multiple clinical consequences, evaluating serum VEGF and using a noninvasive, safe, economic viable method like NFC can be considered useful tools for better understanding of the degree of vascular injury, improving the prognostic values, and applying proper therapeutic measures. However, further studies on a larger numbers of patients are needed to validate the cutoff values of serum VEGF used in detecting SLE disease activity and the value of using NFC in barrel with some clinical manifestations as prognostic factors and for adjusting proper treatment according to regular capillaroscopic examination changes through a long-term follow-up. Moreover, trials of drugs targeting VEGF and its receptors are warranted to verify their possible efficacy in lupus treatment.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 Iman IE, Soha EI, Wael SE, Hanan MF, Amal HE. Assessment of vascular endothelial growth factor in systemic lupus erythematosus patients with anti-phospholipid syndrome. Egypt Rheumatol 2018; 41:1.

2 Ragab O, Ashmawy A, Abdo M, Mokbel A. Nailfold capilloroscopy in systemic lupus erythematosus. Egypt Rheumatol 2011; 33:61–67.

3 Petri M, Orbai AM, Alarcón GS. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus'. Arthritis Rheum 2012; 64:2677–2686.

4 Gladman DD, Ibanez D, Urowitz MB. Systemic Lupus Erythematosus Disease Activity Index 2000. J Rheumatol 2002; 29:288–291.

5 Gladman DD, Goldsmith CH, Urowitz MB, Bacon P, Fortin P, Ginzler E, *et al.* The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus International Comparison. J Rheumatol 2000; 27:373–376.

6 Schips L, Dalpiaz O, Lipsky K, Langner C, Rehak P, Puerstner P, *et al.* Serum levels of vascular endothelial growth factor (VEGF) and endostatin in renal cell carcinoma patients compared to a control group. Eur Urol 2007; 51:168–174.

7 Bărbulescu AL, Vreju AF, Bugă AM, Sandu RE, Criveanu C, Tudoraşcu DR, *et al.* Vascular endothelial growth factor in systemic lupus erythematosus–correlations with disease activity and nailfold capillaroscopy changes. Rom J Morphol Embryol 2015; 56:1011–1016.

8 Cutolo M, Melsens K, Wijnant S, Ingegnoli F, Thevissen K, De Keyser F, *et al.* Nailfold capillaroscopy in systemic lupus erythematosus. A systematic review and critical appraisal. Autoimm Rev 2018; 17:344–352.

9 Kuryliszyn-Moskal A, Klimiuk PA, Sierakowski S, Ciołkiewicz M. Vascular endothelial growth factor in systemic lupus erythematosus: relationship to disease activity, systemic organ manifestation, and nailfold capillaroscopic abnormalities. Arch Immunol Ther Exp 2007; 55:179.

10 Moneib HA, Salem SA, Aly DG, Khedr HT, Wafaey HA, Hassan HE. Assessment of serum vascular endothelial growth factor and nail fold capillaroscopy changes in systemic lupus erythematosus with and without cutaneous manifestations. J Dermatol 2012; 39: 52–57.

11 Liu J, Wang X, Yang X, Ya Q, Wang S, Han W. Investigating the role of angiogenesis in systemic lupus erythematosus. Lupus 2015; 24:621–627.

12 Avihingsanon Y, Phumesin P, Benjachat T, Akkasilpa S, Kittikowit V, Praditpornsilpa K, *et al.* Measurement of urinary chemokine and growth factor messenger RNAs: a noninvasive monitoring in lupus nephritis. Kidney Int 2006; 69:747–753.

13 Ghazali WSW, Iberahim R, Ashari NSM. Serum vascular endothelial growth factor (VEGF) as a biomarker for disease activity in lupus nephritis. Malay J Med Sci 2017; 24:62.

14 Zhou L, Lu G, Shen L, Wang L, Wang M. Serum levels of three angiogenic factors in systemic lupus erythematosus and their clinical significance. BioMed Res Int 2014; 2014:627126.

15 Navarro C, Candia-Zuniga L, Silveira LH, Rui V, Gaxiola M, Avila MC, *et al.* Vascular endothelial growth factor plasma levels in patients with systemic lupus erythematosus and primary antiphospholipid syndrome. Lupus 2002; 11:21–24.

16 Heshmat NM, El-Kerdany TH. Serum levels of vascular endothelial growth factor in children and adolescents with systemic lupus erythematosus. Pediatr Allergy Immunol 2007; 18:346–353.

17 Ciołkiewicz M, Kuryliszyn-Moskal A, Klimiuk PA. Analysis of correlations between selected endothelial cell activation markers, disease activity, and nailfold capillaroscopy microvascular changes in systemic lupus erythematosus patients. Clin Rheumatol 2010; 29:175.

18 Ibrahim FF, Draz HM, Al Sherbeni HH. Serum VEGF and haemoglobin dielectric properties in patients with systemic lupus erythromatosus. J Med Sci 2008; 8:469–476.