The relationship between nailfold capillaroscopic assessment and telangiectasia score with severity of peripheral vascular involvement in systemic sclerosis

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Received on September 22, 2014; accepted in revised form on January 12, 2015.

Clin Exp Rheumatol 2015; 33 (Suppl. 91): S92-S97.

Key words: systemic sclerosis, capillaroscopy, telangiectasia score, peripheral vascular involvement

Competing interests: none declared.

ABSTRACT

Objective. *To determine the association of nailfold video-capillaroscopy (NVC) findings and telangiectasia score with digital ulcer (DU) history and severity of peripheral vascular involvement (PVI) in systemic sclerosis (SSc).*

Methods. *Fifty-nine SSc patients fulfilling Leroy & Medsger criteria were evaluated including telangiectasia score, disease activity and severity scores. NVC was performed according to qualitative (early, active and late patterns) and semi-quantitative assessments.*

Results. *When DU+ and DU- groups were compared; the mean score of capillary number (CN) was 2.0±0.5 vs. 1.4±0.7 (p<0.001), irregularly enlarged capillaries (IEC) was 1.8±0.6 vs. 1.4±0.7 (p<0.05), microangiopathy evolution score (MES) was 2.5±1.5 vs. 1.8±1.0 (p<0.05) and 'early' pattern was significantly less frequent in DU+ patients (1 vs. 9, p=0.016). The frequency of severe-PVI (Medsger severity score of 2–4) was 22% in females (12/54) and 80% in males (4/5). When severe and non-severe groups were compared; the mean score of CN was 2.1±0.4 vs. 1.5±0.7 (p<0.001), MES was 2.8±1.6 vs. 1.8±1.1 (p<0.05) and 'early' pattern was significantly less frequent in patients with severe PVI (0 vs. 9, p=0.049). The mean values of telangiectasia score were similar between groups.*

Conclusion. *DU history and severe PVI in SSc were associated with capillary loss and microangiopathy. 'Early' NVC pattern was very rare in patients with DU history and was not found in severe PVI. Severe PVI in males was more frequent than females. Telangiectasia scores were not found to be related to PVI. NVC may be a helpful method in the assessment of SSc patients for PVI prognosis, warranting prospective studies.*

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterised by autoimmune inflammation, vascular injury and fibrosis (1). Vascular injury starts in the early phases of the disease and can cause digital ischaemia-gangrene and pulmonary arterial hypertension (PAH) which were major factors of high morbidity and mortality in SSc. (2). Raynaud's phenomenon (RP) is accepted as the initial clinical symptom reflecting the microvascular injury before the onset of other manifestations (3, 4).

Microvascular injury induces structural changes of capillary array and can be established by a non-invasive imaging tool, nailfold video-capillaroscopy (NVC), from the early stages of the diasese. Therefore it has been accepted as a useful method for differentiation of primary RP from secondary, early diagnosis of SSc and follow-up of the progression of microangiopathy in SSc (5-8). NVC assessment has been shown to be a reliable method for the prediction of development of digital ulcers (DUs) and severity of the organ involvement (9-13). Improvement in NVC abnormalities after 12 months of treatment with an endotelin receptor antagonist, bosentan, supports that NVC may be also used for establishing the efficacy of treatment (14).

RP and chronic digital ischaemia leading to DUs can be seen in all subsets of disease but more frequent in dcSSc. DUs heal slowly especially when complicated with infections or gangrene (15, 16). Early stages of the SSc were shown to have higher risk of DU development in a French cohort; first DU occured in 43% within 1 year following the first non-Raynaud's symptom and 73% within 5 years (17). Digital lesions also have a tendency to recur. In the study by Nihtyanova *et al*., 1168 SSc

patients analysed, 16.6% had at least one episode of DU and 12% hospitalised at least once for vasodilatory treatments during 18-month period (18).

Telangiectases are one of the most visible clinical manifestations of microvascular pathology composed of vasodilated post-capillary venules in the papillary and superficial reticular dermis of the skin without inflammatory changes (19). They may be found on hands, face, mucosa, limbs and trunk of both of two subgroups of SSc patients. In a study of Shah *et al*., a significant correlation between number of telangiectases and pulmonary vascular disease-PAH was found, but association with other vascular manifestations like digital ulcers or gangrene could not be shown (20).

In this study we determine the association of NVC abnormalities and telangiectasia score (TS) with DU history and severity of peripheral vascular involvement (PVI) in SSc.

Patients and methods

A total of 59 SSc patients with non-RP symptom of <8 years (preferably <2 years) and fulfilling Leroy & Medsger classification criteria (21) were included into the study. Patients with age of <18, non-RP symptom of >8 years and not eligible for performing NVC were excluded. Demographics, onset of symptoms, organ involvement, treatment details, laboratory and imaging findings including serology, echocardiography, respiratory function tests, high-resolution computed tomography (HRCT) of chest were noted into a pre-defined protocol. TS (For each body area including face, hands, arms, chest and abdomen, back, legs and feet; telangiectases were scored as 0 if no telangiectasia was present, 1 if there were fewer than 10 telangiectases, 2 if there were 10 or more telangiectases, the total possible telangiectasia score was 22 (20), modified Rodnan skin score (MRSS), Valentine activity score (VAS) (different scores of 10 parameters, the total possible VAS score was 10) (22) and Medsger severity score (SS) [Score of 0 to 4 for 9 involvements, the total possible SS score was 36. PVI was scored as 0 if no RP or not requiring vasodilators, 1 if RP requiring vasodilators, 2 if digital pitting scars, 3 if DU, 4 if gangrene was present] (23) were evaluated simultaneously with NVC.

NVC was performed on all patients after 20 minutes of resting time period in a separate room with a constant temperature of 20–22°C by a video-capillaroscopy (Optilia, Mediscope-Digital Video Microscope). OptiPix (2010, Version:1.2.0) programme was used to store the images. The investigator (YY) who recruited patients into the study and evaluated medical records, performed NVC studies. After a drop of cedar oil on the nailfold, at least 2 representative images for each of second to fifth fingers of left and right hands were captured with the 200x optical probe. All images (16 images for 8 fingers) were stored and examined later by a second investigator (MI) under blinded conditions. Number of capillaries (CN), irregularly enlarged capillaries (IEC), giant capillaries (GC), microhaemorrhages (H), capillary ramifications (CR), capillary array disorganisation (CAD) and maximum capillary diameter were calculated per 1 millimeter (mm) area of the images.

Firstly, NVC assessed qualitatively. Sclerodermic NVC pattern (early or active or late pattern) was investigated and decided as follows: early NVC pattern, few giant capillaries (homogeneously enlarged loop with a diameter >50 μm), few capillary haemorrhages (dark mass due to haemosiderin deposit), regular capillary distribution and no significant loss of capillaries (at least 9–10 capillaries per linear mm counted at the distal row of the nailfold); active NVC pattern, frequent giant capillaries, frequent capillary haemorrhages, moderate loss of capillaries, mild disorganisation of the capillary architecture (irregular capillary distribution and orientation with respect to the nailfold along with shape heterogeneity of the loops), absent or mild ramified capillaries (branching, bushy or coiled capillary often originating from a single normal sized capillary); late NVC pattern, irregular enlargement of capillaries, few or absent giant capillaries and capillary haemorrhages, severe loss of capillaries with avascular areas, disorganisation of the normal capillary array, ramified/bushy capillaries (9).

Secondly, NVC assessed semi-quantitatively and scoring of the capillary abnormalities (CN/IEC/GC/H/CR/CAD) (score:0–3) was performed as follows: 0 = no changes, 1 = less than 33% of capillary alterations/reduction, 2 = 33–66% of capillary alterations /reduction, 3 = more than 66% of capillary alterations/reduction, per linear mm at the distal row of the nailfold. Microangiopathy evolution score (MES) was the sum of CN, CR and CAD scores. The mean score for each capillary abnormality was calculated from the average score of two images of 1 mm of each 8 digits (2^{nd}, 3^{rd}, 4^{th} and 5^{th} fingers of both hands), added together, and then the final value divided by eight to obtain the score (10).

The study was approved by local ethics committee and informed consent was obtained from all participants.

For statistical analysis of the data 'SPSS version 16 for Windows' programme was used. Groups were compared with Pearson chi-square/Fisher's tests for categorical variables or student's *t*- and Mann Witney U-tests for continuous variables. Results were presented as mean ± standard deviation (±SD). *P*-values less than 0.05 were considered significant. The distribution and median levels of NVC abnormalities and TS in patient groups according to DU history and severity of vascular involvement are summarised in boxplot graphics.

Results

Demographics and clinical characteristics of SSc patients were summarised in Table I.

The mean age of the patients was 45.6 and 91.5% were females. The mean duration of RP, non-RP symptoms (NRP) and skin involvement were 6.1±6.5, 3.1±2.0 and 3.0±2.0 years, respectively. Of the patients 34% were diffuse, 66% were limited cutaneous; 22% were anti-centromere(+) and 49% were anti-Scl70(+). Smoking habitus (active or ex-smoker) was 46%. RP (97%), gastrointestinal involvement (72%), telangiectases (58%), arthritis (49%) and DU (46%) were frequent manifestations in SSc cohort. Calcium

Table I. Demographics and characteristics of SSc patients.

		SSc Patients (n=59)
Age (mean ± SD)		45.6 ± 11.5
Female sex (n) (%)		54 (91%)
Duration of RP (year) (mean ± SD)		6.1 ± 6.5
Duration of non-RP symptom (year) (mean ± SD)		3.1 ± 2.0
Duration of skin involvement (year) (mean ± SD)		3.0 ± 2.0
Smoking history(n) (%)		27 (46%)
Skin	Diffuse cutaneous SSc (dcSSc) (n) (%)	20 (34%)
Involvement	Limited cutaneous SSc (lcSSc) (n) (%)	39 (66%)
Serology (n) (%)	ANA (+)	54 (92%)
	Anti-centromere (+)	13 (22%)
	Anti-Scl70 (+)	29 (49%)
Organ(n) (%)	Raynaud's	57 (97%)
Involvement	Digital ulcer history	27 (46%)
	Telangiectases	34 (58%)
	Arthritis	29 (49%)
	Renal crisis	4 (7%)
	Flexion contracture-t.friction rubs	9-5 (15-9%)
	Dysphagia-reflux-diarrhoea	43 (72%)
	FVC<%80-DLCO<%80	14-23 (24-39%)
	Pulmonary fibrosis	10 (17%)
	Pulmonary hypertension	4 (7%)
Treatment(n) (%)	No treatment (recent diagnosis)	11 (19%)
	Calcium channel blockers-PPI	46-46 (78-78%)
	Acetylsalicylic acid	37 (63%)
	Ilioprost	3 (5%)
	Immunosuppressives	36 (61%)
	Steroids	29 (49%)

Table II. NVC Patterns between different groups of peripheral vascular involvement.

NVC patterns	Peripheral vascular involvement			
	DU history+ (n=27)	DU history- (n=32)	PVI-severe (n=16)	PVI-non-severe (n=43)
Early	1*	9	0*	10
Active	14	16	9	21
Late	12	7	7	12
Total	27	32	16	43

*p<0.05, when DU+ and DU- groups were compared, when severe and non-severe PVI groups were compared with Chi-square tests.

Table III. Semi-quantitative scoring of NVC parameters between different groups of peripheral vascular involvement.

Scores of NVC parameters	Peripheral vascular involvement (PVI)			
	DU history+ (n=27)	DU history- (n=32)	PVI-severe (n=16)	PVI-non-severe (n=43)
Capillary reduction	2.0 ± 0.5**	1.4 ± 0.7	2.1 ± 0.4**	1.5 ± 0.7
Irregularly enlarged capillaries	1.8 ± 0.6*	1.4 ± 0.7	1.6 ± 0.6	1.6 ± 0.7
Microangiopathy evolution score	2.5 ± 1.5*	1.8 ± 1.0	2.8 ± 1.6*	1.8 ± 1.1

*p<0.05, **p<0.001 when DU+ and DU- groups were compared, when severe and non-severe PVI groups were compared with Mann Whitney U and student's *t*-tests

channel blockers (78%), acetylsalicylic acid (63%) and ilioprost (5%) were the treatments for PVI (Table I).

When we compared the patients according to presence of DU history (DU+ or DU-); demographics, duration of symptoms, serology, organ involvements and treatments were similar between groups. NVC patterns and semi-quantitative scoring of NVC parameters were summarised in Table II and Table III. Early NVC pattern was significantly less frequent in DU+ patients (1 *vs*. 9, p=0.016). Active and late patterns were frequent in all group but similar between DU+ and DU- patients. The mean scores of CN, IEC and MES were significantly higher in DU+ patients (2.0±0.5 *vs*. 1.4±0.7, p<0.001, 1.8±0.6 *vs*. 1.4±0.7, p=0.029 and 2.5±1.5 *vs*. 1.8±1.0, p=0.041, respectively).

Patients were grouped according to their current PVI status as severe (SS;2-4) (n=16) or non-severe (SS;0-1) (n=43). Demographics, duration of symptoms, serology, organ involvements and treatments were similar between groups. Severe PVI was found to be more frequent in males (4/5, 80% *vs*. 12/54, 22%, p=0.017). When we compared severe and non-severe PVI groups; early sclerodermic pattern was significantly less frequent in patients with severe PVI (0 *vs*. 9, p=0.049) (Table II). Active and late patterns were frequent but similar between groups. The mean scores of CN and MES were significantly higher in patients with severe-PVI (2.1±0.4 *vs*. 1.5±0.7, p<0.001 and 2.8±1.6 *vs*. 1.8±1.1, p=0.038) (Table III). Distribution and median levels of scores significantly different between groups according to DU history and severity of RP were summarised in Figure 1.

The mean values of TS was not statistically different between groups (Table IV; Fig. 2). TS was correlated only with duration of non-RP sypmtom (r=0.407, p=0.021) in DU- group.

The mean values of MRSS, VAS and SS were not statistically different between groups (Table IV; Fig. 2). In DU+ group; scores of ramification and disorganisation were correlated with activity and severity (r=0.396/p=0.041 and r=0.702/p<0.001, r=0.451 /p=0.018 and r=0.712/p<0.001, respectively), capillary loss and microangiopathy were correlated with severity (r=0.530/p=0.004 and r=0.611/p=0.001). In DU- group; scores of capillary loss, ramifications, disorganisation and microangiopathy were correlated with activity (r=0.427/p=0.015, r=0.750/p<0.001, r=0.370/p=0.037 and r=0.673/p<0.001) and scores of capillary loss, giants, ramification and microangiopathy were correlated with severity (r=0.400/p=0.023, r=0.357/p=0.045, r=0.779/p<0.001 and r=0.696/p<0.001).

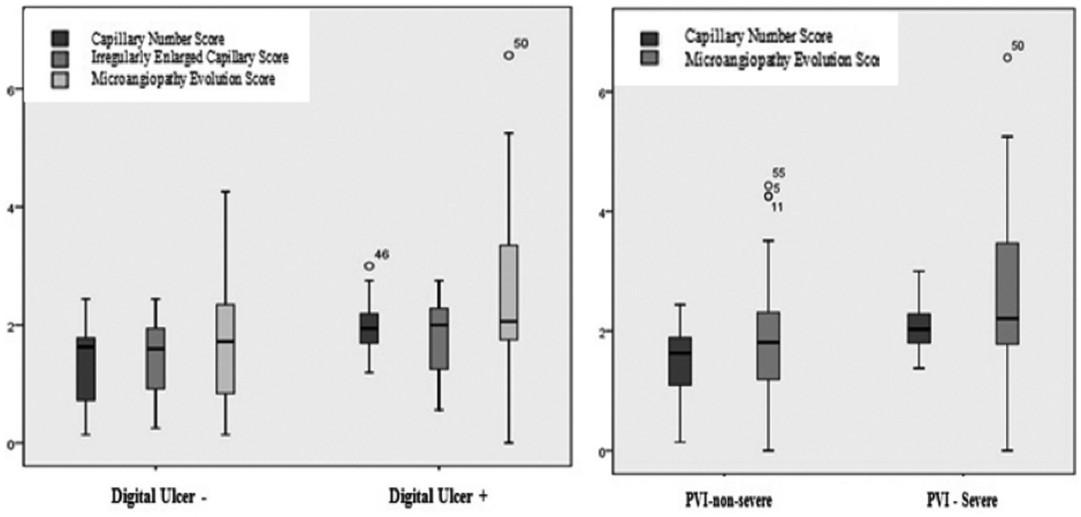

Fig. 1. The distribution and median scores of NVC in groups according to presence of DU and severity of PVI.

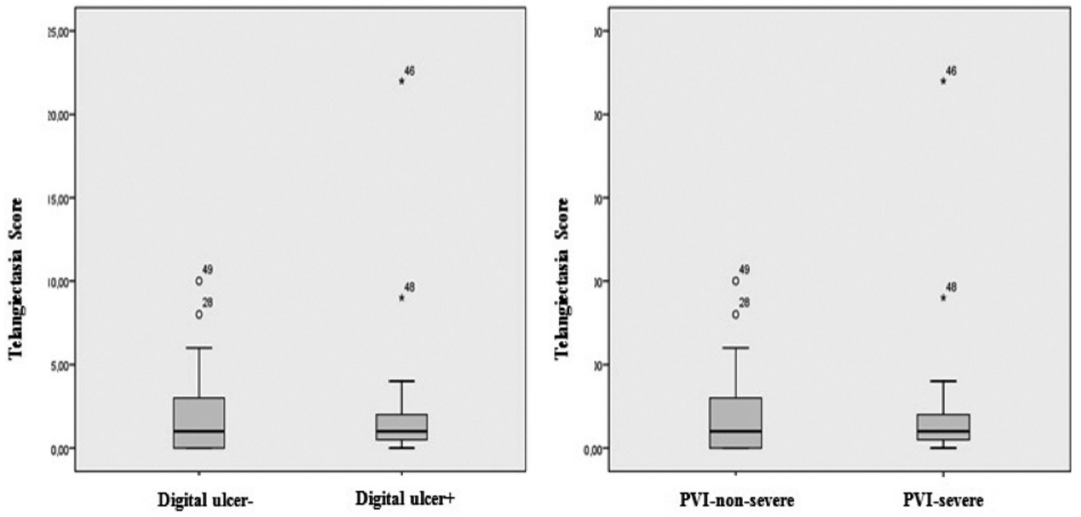

Fig. 2. The distribution and median levels of telangiectasia score in groups according to presence of DU and severity of PVI.

Discussion

In this prospective study, we evaluated the relationship between different microvascular manifestations of SSc; telangiectases, ischaemic digital lesions and capillaroscopic changes reflecting microangiopathy to identify the tools and/or markers for earlier approach. Early diagnosis and treatment in SSc have to be the goal to prevent organ damage and progression in such a chronic disease with high morbidity and mortality. The period of the progression of RP to the skin and organ involvements was found to be varying 1.9 to 4.8 years in diffuse and limited cutaneous subgroups of SSc (24). The new classification criteria for SSc included RP, DU, PAH, interstitial lung disease, telangiectasia, puffy fingers/sclerodactily, specific antibodies and sclerodermic capillaroscopic patterns to capture early SSc and SSc without significant skin involvement to allow earlier approach (25).

DUs (46%) and telangiectases (58%) were frequent manifestations in our patient group as in reported large cohorts (26). Increasing number of DUs (especially ≥3) were found to have higher proportions of diffuse cutaneous involvement and lung fibrosis, more impairment in work and functional activities in SSc (27). SSc patients were grouped according to DU history and severity of current PVI, NVC was assessed qualitatively and semi-quantitatively. The frequency of severe PVI was higher in male patients (80% *vs.* 22%, p=0.017), who were represented

Table IV. The mean values of Telangiectasia, Modified Rodnan Skin score (MRSS), Valentini Activity and Medsger Severity scores between different groups of peripheral vascular involvement.

	Peripheral vascular involvement						
	SSc (n=59)	DU+ (n=27)	DU- (n=32)		PVI-severe (n=16)	PVI non-severe (n=43)	
Telangiectasia score	2.3±3.5	2.7±4.7	1.9±2.1	p=0.78	3.0±5.5	2.0±2.4	p=0.85
MRSS	8.8±7.9	9.2±7.3	8.4±8.5	p=0.11	9.9±9.1	8.3±7.5	p=0.69
Valentini Activity score	1.5±2.1	1.9±2.1	1.2±2.0	p=0.11	2.1±2.4	1.3±1.9	p=0.19
Medsger Severity score	4.6±2.7	4.7±2.2	4.5±3.0	p=0.09	5.1±2.4	4.4±2.7	p=0.07

with active DUs at time of diagnosis. Increased severity of peripheral vasculopathy in males has been reported previously in SSc (28).

When NVC patterns were evaluated in the subgroups; early sclerodermic pattern was significantly less frequent in patients with DU+ and severe PVI. 'Early' pattern was the less related pattern to the presence of DU and severe PVI, which was similar to reported qualitative NVC assessments before. Late sclerodermic pattern was found to have significant relationship with digital ulcers and other organ involvements. Active/late patterns were more frequent in the clusters with organ involvement and moderate/severe MRSS in a large SSc group of EUSTAR study (29). In the study by Smith *et al*; sclerodermic patterns were related with future severe PVI (p=0.003) and pulmonary (p=0.001) disease development at 18–24.months. Worsening capillaroscopic patterns; early, active and late, were found to predict future PVI and pulmonary involvement when compared with normal pattern (odds ratios were 2.5, 6.4 and 16.1 for PVI and 2.3, 5.4 and 12.7 for pulmonary involvement, respectively) (13). Active/late patterns were associated with DU and severe-PVI in our cohort but we can not conclude about the predictive value of NVC for future DU and severity of PVI due to cross-sectional design of our study.

Previously, NVC was used for the evaluation of the efficacy of treatment. Late sclerodermic patterns, including large avascular areas, severe capillary loss and capillary array disorganisation changed to active pattern with disappeared avascular areas and new microhaemorrhages, in seven patients at 12.month of bosentan treatment used for PAH (14). Another study with a small number of SSc patients reported some capillaroscopic changes after iloprost used for PVI (30). These studies revealed that transition of patterns can be observed by specific treatments. We could not identify any capillaroscopic changes related with treatment due to small number of patients treated with specific therapies for PVI and cross-sectional study design.

The semi-quantitative scoring of NVC parameters showed that the mean scores of CN and MES were higher in patients with DU+ (p<0.001 and p=0.041) and severe-PVI (p<0.001 and p=0.038). Score of capillary loss (CN) and microangiopathy were related with presence of DU and severity of PVI in our cohort. Different scoring methods of capillaroscopic parameters identifying scleroderma patterns were used to evaluate vascular disease in SSc. In the study evaluating the prediction of the onset of new DU by NVC, capillaroscopic skin ulcer risk index (CSURI) calculated with capillary numbers, giant capillary numbers and capillary diameter parameters, was found to have high specificity and sensitivity to predict the risk of DU (12). In another study by Riccieri *et al*., it was reported that patients with PAH had frequently active or late patterns, NVC score of >1 and avascular area staging >1 (p=0.03, p=0.03 and p=0.003, respectively) than those without PAH. In addition, these scores were found to be correlated with mean PAP levels (31). PAH was observed in only 4 patients of our study which was insufficient to analyse. Kayser C *et al*. studied the NVC abnormalities as a predictor of mortality in SSc and showed the association between increased risk of death with avascular score higher than 1.5 (HR:2.265). Survival rates at 1,5 and 10 years were found to be 97%, 86% and 59% in patients with avascular score higher than 1.5 and 97%, 97% and 91% in patients with avascular score ≤1.5, respectively. This study revealed the decreased survival in patients with severe capillaroscopic changes analysed by semi-quantitative assesment of NVC (32).

Telangiectasia, a non-inflammatory microvascular change commonly seen in SSc, related to vascular injury and/or inadequate vascular repair. In SSc, to study the relationship between telangiectases and the severity of PVI might be important because of possible common pathogenetic mechanisms. In the study of Ennis *et al*., patients reporting telangiectases were shown to be more likely to have severe digital ischaemia than those not (33). A score described for evaluating telangiectases, telangiectasia score (TS) in the study of Shah, et al., was found to be associated with the presence of pulmonary vascular disease (20). In this study, TS was correlated with only duration of non-Raynaud sypmtom in patients without DU history. We did not find any relation between TS with positivity of DU or severity of PVI.

Scores of certain capillaroscopic abnormalities including ramification and disorganisation significantly correlated with disease activity and severity. Capillary loss and microangiopathy correlated with only disease severity in the DU+ group. Scores of capillary loss, ramification and microangiopathy significantly correlated with disease activity and severity even in patients without a history of DU confirmed that these parameters should be carefully evaluated in follow-up period to recognise the patients with higher risk of developing severe SSc.

There are limitations of our study that should be mentioned. This is a cross-sectional study in a relatively small group of SSc patients and a longitudinal follow-up to evaluate the progress of peripheral vascular and other involvements by NVC is necessary. We did not perform any analysis according to number DUs. For this study, interobserver aggreement for the analysis of capillaroscopic parameters have not been evaluated by statistical analysis rather we have decided on the final scoring by consensus.

In conclusion; in this study we evaluated the relationship between telangiectases, ischaemic digital lesions and capillaroscopic changes reflecting microangiopathy in SSc patients with relatively early disease. Severe PVI in males was more frequent than females. 'Early' NVC pattern was very rare in patients with DU history and was not found in patients with severe PVI. DU history and severe PVI were associated with capillary loss and microangiopathy. Correlations between severe capillaroscopic changes such as capillary loss, ramifications and microangiopathy with disease activity and severity in all patients with or without peripheral vascular involvement show that NVC abnormalities may help clinicians to predict the patients with higher risk of

severe disease to allow early treatment. Telangiectasia score was not found to be related to PVI and possibly not helpful in the prediction of PVI. NVC was found to be a useful tool in the assessment of SSc patients for PVI prognosis and an essential method for research of microvascular pathology, warranting prospective studies in a large number of patients.

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