Nailfold Capillaroscopic Changes in Dermatomyositis and Polymyositis Egyptian Patients: Relation to Disease Activity

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ABSTRACT

Background: Nailfold capillaroscopy (NFC) has been described to be a valuable instrument used in diagnosis of systemic sclerosis (SSc) and juvenile dermatomyositis (JDM) patients. Though, NFC has been infrequently assessed in adult dermatomyositis (DM) patients.

Objectives: Our aim was to visualize nailfold capillary changes in dermatomyositis (DM) and polymyositis (PM) Egyptian patients and to identify a specific diagnostic capillary pattern and to assess its relevance to disease activity, clinical and laboratory findings.

Patients and Methods: This study included 20 patients (12 DM, 5 PM, and 3 overlap syndrome). Routine laboratory assessment was done, disease and skin activity scores were evaluated. Assessment of the nailfold capillary circulation using the videocapillaroscope was done and capillary density score was assessed.

Results: The mean age was 39±12 years and their mean disease duration was 24±19 months. The mean muscle disease activity score was 3.8±3.3, and global disease activity score (DAS) 3.92±3.09. The mean skin activity score was 2±3. The global DAS was significantly higher in patients with branched capillaries (p=0.041). Skin activity score was significantly higher in patients with capillary hemorrhage (p=0.024). More severe capillaroscopic findings were prominent in DM patients rather than PM or overlap patients.

Conclusion: Capillary branching is more common in patients with higher global DAS and capillary hemorrhage is more frequent in patients with higher skin activity score. Capillaroscopic changes are evident in DM patients rather than PM or overlap patients.

Keywords: Nailfold capillaroscopy, Dermatomyositis, Polymyositis, Disease activity.

INTRODUCTION

Nailfold capillaroscopy (NFC) is a highly sensitive, low-cost, simple, harmless, and noninvasive imaging tool used in the morphological examination of nutritious nailfold capillaries [(1)]. It is an important vascular imaging method that allows for in vivo direct visualization of the microcirculation, with a definite expecting role in distinguishing Raynaud's phenomenon patients who are at risk of developing into the spectrum of scleroderma disorder, specially systemic sclerosis (SSc), systemic lupus erythematosus (SLE), dermatomyositis (DM) and small vessels vasculitis [(2)].

Idiopathic inflammatory myositis (IIM) is an acquired muscle disorder, with diverse manifestations, which occurs in different age groups. A common feature of IIM is immune mediated muscular inflammatory changes leading to weakness. Though, variabilities in clinical picture, prognosis, histology, and immunopathology enable distinguishing main three diseases: dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM). Dermatomyositis is recognized as a type of microangiopathies which is complement mediated, that has multiple clinical consequences, clinically the disease is marked by skin manifestations: an erythematous rash on the face and neck, heliotrope rash, Gottron papules, with or without muscle weakness. On the other hand, polymyositis is believed to occur clinically as a sub-acute myopathy, with different degrees of muscle weakness, which is mediated by cytotoxic T cells. Extra-muscular clinical features are designated in both DM and PM, like cardiac involvement, arthralgias, interstitial pulmonary disease, and the relationship to malignancies associated with dermatomyositis [(2)].

The blood vessels destruction and profound internal organ dysfunctions occur as a result of chronic systemic inflammation associated with injury of the vascular endothelium. Thus, earlier recognition of vascular affection has an important value in the diagnosis of different connective tissue diseases (CTDs) [(3)].

The frequency of NFC microvascular changes in DM and PM patients, typical features and the relationship to disease activity, as well as the possibility of its association with clinical and laboratory parameters are not well recognized [(2)]. This study was performed to visualize nailfold capillary changes in DM and PM Egyptian patients and to identify a specific capillary pattern and to assess its

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relationship to disease activity, clinical and laboratory findings.

PATIENTS AND METHODS

In this observational cross-sectional study, 20 (12 DM, 5 PM, and 3 overlap) patients; diagnosed according to "2017 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups" were involved [(4)]. Patients were randomly recruited from rheumatology outpatient clinic and inpatient department, Ain Shams University Hospital. Regarding age, all subjects were over 16 years. Hypertensive and/or diabetic patients were excluded from the study. Patients were recruited from February 2018 to September 2019.

Ethical approval

This study was approved by the Faculty of Medicine at Ain Shams University, Local Research Ethical Committee. All patients included in this study provided written informed consent to contribute in the study.

Full history taking was done with stress on disease activity symptoms, and medications. Disease activity was evaluated with the Myositis Disease Activity Assessment (MYOACT),Visual Analog Scale (VAS) section of Myositis Disease Activity Assessment Tool (MDAAT) [(5)], skin activity score was assessed using the visual analog scale (VAS) [(5,6)], and global disease activity score (DAS) was evaluated [(7)].

Laboratory assessment was done; complete blood count by Coulter, erythrocyte sedimentation rate (ESR) in first hour estimated by Westergren method, quantitative C- reactive protein (CRP) done by immunoturbidimetry. Liver enzymes, urinalysis and tests for kidney functions were estimated. Serum creatine kinase (CK) was measured by the forward reaction. Diagnostic electromyography (EMG), muscle biopsy, and muscle images: ultrasound (US) and muscle magnetic resonance imaging (MRI) were assessed when necessary. Chest radiographs, high-resolution computed tomography scans and pulmonary function tests were done when indicated.

Assessment of the nailfold capillary circulation using the videocapillaroscope (Videocap 3.0, DS Medica, Milan, Italy), by the same experienced examiner who was blinded to both clinical and laboratory findings. A droplet of immersion oil was put on the nailfold area for resolution improvement, and assessment of all four fingers' nailfold beds was done. Determination of nailfold capillary density was done by calculating the whole number of capillaries in the length of a one millimeter of each finger and calculation of the mean of fingers [(8)].

The normal capillaries are shaped like the upside-down English letter 'U', hair pin like with a thinner arterial limb, an upper part, and a venous limb which is larger than the upper part as illustrated in figure (1) [(8)].

In normal population, the capillaries have homogeneous shape, color, and size, with transverse organization across the cuticle (Figures 2, 3) [(9,10)]. Capillary loops could show distinct morphological alterations, like crossed or twisting loops (with interweaving), subpapillary venous plexus can be reported in nearly 30% of the populace. A minor number of capillary dilatations (ectasia) might be also reported. Small areas of micro-bleeding with focal distribution could be seen in normal subjects, related to ordinary microtrauma [(10)].

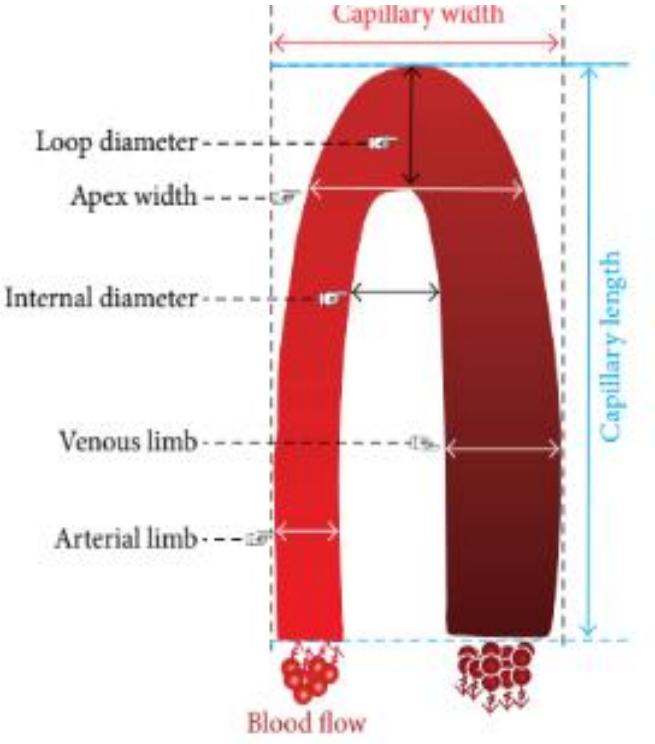

Figure (1): Schematic drawing of the front portion of a nailfold capillary loop [(8)].

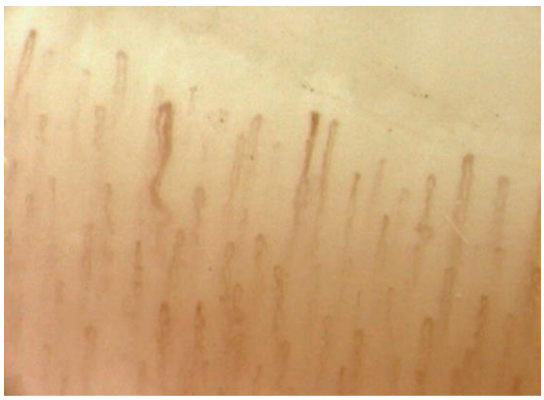

Figure (2): Normal nailfold capillaroscopic pattern with U-shaped capillaries [(9)].

Figure (3): Normal nailfold capillaroscopic findings in a 33-year-old male patient with PM.

With regards to earlier studies, the following nailfold capillaroscopic findings were counted: capillary density (less than seven capillary loops per mm were thought to be atypical); variations in length of capillaries (longer or shorter capillaries); presence of morphological changes like; enlarged, meandering, tortuous, or branched capillaries; micro-hemorrhages; and asymmetrical distribution of the capillary arrays. Diagnostic capillaroscopic patterns were grouped into; *Non-scleroderma like pattern*; which include: normal pattern (homogeneous capillary distribution in the nailfold plexus with no morphological changes and no capillary loss) and non-specific form that lacks complete scleroderma pattern criteria (Figures 2, 3) and *scleroderma like pattern*; defined by "the presence of 2 or more of the subsequent abnormalities: enlarged capillaries, hemorrhages (more than 2 punctuate hemorrhages for each finger, or confluent hemorrhage areas), disorganization of the normal capillary distribution, moderate or widespread capillary loss (i.e. avascular areas) and tortuous, crossed and/or branched capillaries" [(11)] (Figures 4,5).

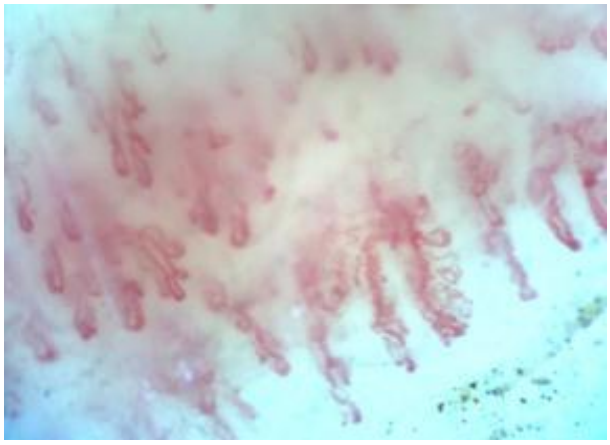

Figure (4): Nailfold capillaroscopic findings in a 39-year-old female with DM showing: cauliflower appearance of enlarged and branched capillaries.

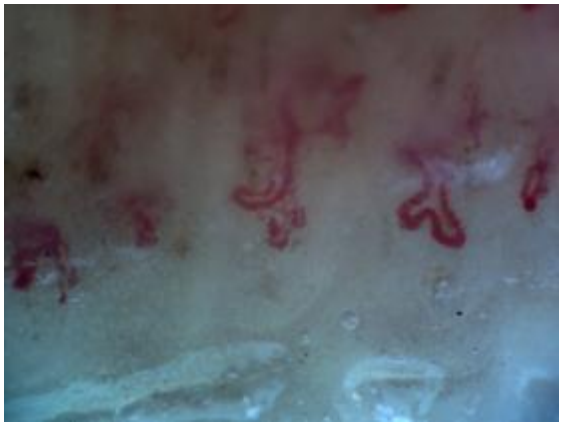

Figure (5): Nailfold capillaroscopic picture showing: giant and branched capillaries, hemorrhage with capillary loss.

Capillary density score was assessed by capillary density score: (the direct observation method) is "the sum of capillaries counted along one linear millimeter of a nailfold's distal row, and calculation of the mean of fingers. The resultant value is the score for each evaluated capillaroscopic parameter (0-3)" [(8,12,13)].

Statistical analysis

Analysis of the collected data was performed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA). Qualitative data were introduced as number and percentages whereas quantitative data were presented as mean, standard deviations and ranges. The comparative studies between 2 quantitative data groups were examined by *t-test* and *Chi-square test* or *Fisher's exact test* was used for qualitative data. Diagnostic accuracy of continuous variables was examined using *Receiver operator characteristic curve (ROC) analysis*. P-value ≤ 0.05 was considered significant.

RESULTS

Twenty patients were studied, seventeen were females. Twelve patients had DM; five had PM; and three were DM/PM/CTD overlap; two had DM overlapping with SLE, one had PM/SSc overlap. The mean age was 39±12 years (16–63 years), their mean disease duration was 24±19 months (2 months to 6 years) (Table 1). The most frequent clinical feature was muscle weakness and the least frequent were cough and Raynaud's phenomenon. Interstitial lung disease was found in 6 (30%) patients, 4 of them had DM and 2 had PM (Table 2). Regarding medications; 20 (100%) patients were receiving oral steroids, 5 (25%) had history of receiving methylprednisolone, while 17 (85%) were receiving azathioprine, 3 (15%) were on methotrexate therapy and 1 DM patient was on mycophenolate mofetil (MMF) during the study period (Table 1).

Table (1): Demographic characteristics of the study population

Variable		N	%
Gender	Male	3	15.0%
	Female	17	85.0%
Disease duration	≤6 months	6	30.0%
	>6 months	14	70.0%
Disease subtype	Dermatomyositis	12	60.0%
	Polymyositis	5	25.05
	Overlap syndrome	3	15.0%
Treatment	Prednisolone	20	100.0%
	Azathioprine	17	85.0%
	Methotrexate	3	15.0%
	Methylprednisolone	5	25.0%
	MMF	1	5.0%

Table (2): Clinical characteristics of the study population

Variable		N	%
Systemic manifestations	Fever	3	15.0%
	Fatigue	13	65.0%
	Weight loss	10	50.0%
	Interstitial lung disease	6	30.0%
	Shortness of breath	2	10.0%
	Cough	1	5.0%
	Abdominal pain	2	10.0%
	Dysphagia	6	30.0%
	Tachycardia	2	10.0%
	Raynaud's phenomenon	1	5.0%
Musculoskeletal manifestations	Arthritis	5	25.0%
	Arthralgia	14	70.0%
	Myalgia	12	60.0%
	Myositis*	12	60.0%
	Muscle weakness#	15	75.0%

*Myositis (proximal myopathy) was defined as an inability to sustain maximal shoulder abduction and hip flexion against the resistance applied by the examiner.

#Muscle weakness refers to residual (>6 months) proximal muscle weakness in patients with normal serum enzyme levels.

The mean muscle disease activity score was 3.8±3.3 (0–9), and global disease activity score (DAS) 3.92±3.09 (0-8.5). Patients with DM had highest values of disease activity score (4.41±3.39), followed by overlap syndrome patients (4.00±2.65), then PM patients (2.70±2.77). The mean skin activity score was 2±3 (0-7), active skin lesions were found in five of the DM patients; one of them had digital ulcers and calcifications.

Regarding NFC among the 20 patients: 16 (80%) showed scleroderma like pattern. Scleroderma like pattern was found in all patients with DM, in 2 (66.7%) patients with overlap syndrome (OS) and in 2 (40%) of PM patients. Enlarged capillaries was the most frequent capillaroscopic findings and the least common was subpapillary venous plexus (Table 3).

Table (3): Capillaroscopic findings of the study population

Variable		N	%
Capillaroscopic findings	Enlarged capillaries	19	95.0%
	Dilated capillaries	11	55.0%
	Avascular areas	11	55.0 %
	Hemorrhage	9	45.0%
	Giant capillaries	8	40.0%
	Disorganized capillaries	7	35.0%
	Branched capillaries	6	30.0%
	Tortuous capillaries	4	20.0%
	Venous plexuses	1	5.0%
	Capillary density score		
	>9 cap/mm² =0 score	9	45.0%
	7-9 cap/mm² =1 score	7	35.0%
	4-7 cap/mm² =2 score	4	20.0%
	<4 cap/mm² =3 score	0	0.0%
Number of scleroderma criteria	Nil	1	5.0%
	One criterion	3	15.0%
	Two criteria	7	35.0%
	Three criteria	8	40.0%
	Four criteria	1	5.0%
Scleroderma pattern	No scleroderma pattern	4	20.0%
	Scleroderma pattern	16	80.0%

Data are number (N) and percentage (%).

The global DAS was higher significantly in the patients who had capillary branching than those without branched capillaries (Figure 6), while there were no significant differences with other capillaroscopic parameters. Skin activity score was significantly higher in patients with capillary hemorrhage than those without capillary hemorrhage (Figure 7).

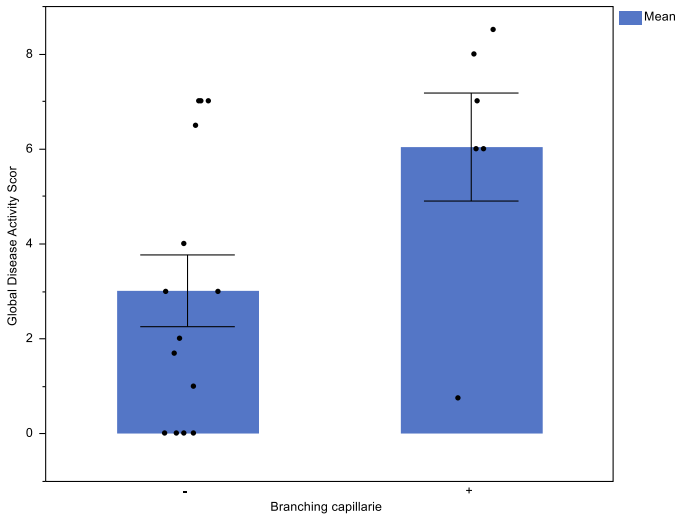

Figure (6): Mean of global disease activity score is significantly higher in patients with branched capillaries than those without branched capillaries (p=0.041).

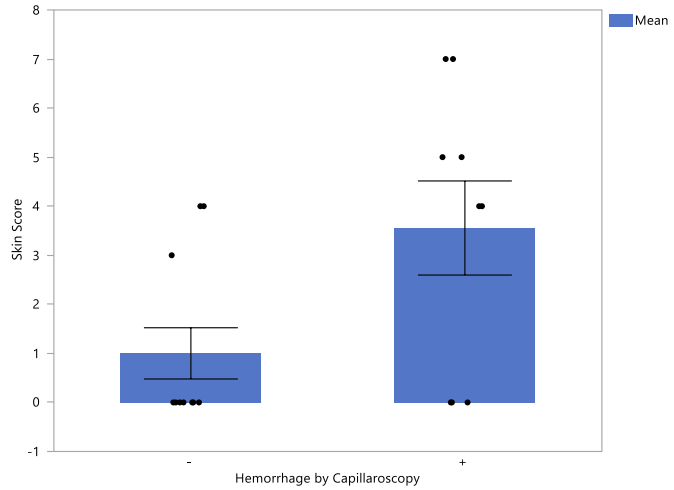

Figure (7): Mean of skin activity score is significantly higher in patients with capillary hemorrhage than those without capillary hemorrhage (p=0.024).

Regarding medications, there were no significant differences between patients who received methotrexate or azathioprine as regard different capillaroscopic findings.

Capillary enlargement was nearly found in all disease subtypes (DM, PM and overlap), giant capillaries (P=0.008), capillary hemorrhage (p=0.026) and avascular areas (p=0.001) were significantly higher in DM patients in comparison to PM and overlap patients. Also, scleroderma like pattern was significantly higher in dermatomyositis patients (p=0.021) than polymyositis and overlap. Whereas branched capillaries only found in DM, but the percentage was not statistically significant (p=0.065). Overall, more severe capillaroscopic findings were prominent in DM rather than the other two groups. We found that, there was no significant difference between patients with or without interstitial lung disease as regard different capillaroscopic findings.

In the present study we evaluated the accuracy of NFC changes -suggested by ***Maricq et al.,*** [(14)] for the diagnosis of DM and PM capillary pattern in our patients, using receiver operator characteristic curve (ROC). We have found that the sensitivity and specificity for NFC different changes were variable (as shown in table 4).

Table (4): Accuracy of NFC changes for the diagnosis of DM and PM capillary pattern

NFC changes	Sensitivity %	Specificity %
Capillaries enlargement	100%	25%
Dilated capillaries	50%	25%
Giant capillaries	50%	100%
Tortuosity	25%	100%
Branched capillaries	38%	100 %
Capillaries loss (avascular areas)	69%	100%
Disorganized capillaries	31%	50%
Capillary hemorrhage	56%	100%

NFC: nailfold capillaroscopy, DM: dermatomyositis, PM: polymyositis.

DISCUSSION

The current study was designed to evaluate capillary changes in Egyptian DM and PM patients and to identify a specific capillary pattern and to assess its relationship to disease activity, clinical and laboratory findings. The frequency of different nailfold capillaroscopic changes in DM patients was assessed by several studies. Our results agree with the following studies; **Mercer *et al.*** [(15)] who studied twenty-four patients diagnosed as IIM (14 polymyositis, 6 dermatomyositis, 4 overlap syndrome), they reported that enlarged capillaries, branched capillaries and avascular areas were highly frequent.

Also, **Miossi *et al.*** [(16)] who examined 39 DM patients and reported that NFC changes in these patients were as follows: 89.7% had branching capillaries, 87.2% had dilated capillaries, 61.5% had giant capillaries, 43.6% had severe avascular areas, and 15.4% showed high degree of micro-hemorrhages. Another study done by **Selva-O'Callaghan *et al.*** [(17)] reported that microhemorrhages and capillary enlargement were the most frequent NFC changes in patients with PM/DM. Again, our results regarding the capillary pattern in PM and DM patients were consistent with **Manfredi *et al.*** [(2)] who found that enlarged and giant capillaries, capillary loss, disarray

of vascular architecture, and branched capillaries were the most frequent NFC findings in 29 DM and 24 PM patients.

Scleroderma like pattern was defined according to **Maricq *et al.*** [14] with adjustments according to **Bergman *et al.*** [18] "NFC pattern includes the presence of two or more of the following findings in at least two nail folds: enlarged capillaries, hemorrhages (more than two punctate hemorrhages per finger, or confluent hemorrhage areas), disorganization of the normal capillary distribution, moderate or extensive capillary loss (i.e. avascular areas) and tortuous, crossed and/or ramified capillaries". In the current study this definition was applied. The scleroderma like pattern was 80%. The result agrees with that of **Mugii *et al.*** [11] who reported that 74% of dermatomyositis patients showed the NFC scleroderma like pattern, of **Miossi *et al.*** [16] who found that scleroderma like pattern was 87.1% and by **Wu *et al.*** [19] were 60% had NFC were scleroderma like pattern.

Another definition was considering scleroderma like pattern as a set of typical nailfold capillaroscopic abnormalities characterized by the occurrence of enlarged capillaries (mega-capillaries and/or ectasia), loss of capillary loops, with subsequent decrease in the capillary numbers, micro-bleeding and neo-angiogenesis (ramified capillaries). This concept of scleroderma like pattern was applied by **Souza and Kayser** [20], as scleroderma pattern was detected in about 20–60% of dermatomyositis and polymyositis patients, where DM patients had more frequent findings than PM patients. The same definition was used by **Manfredi *et al.*** [2]; who reported that 39.6% of IIM patients had scleroderma-like pattern. All the above studies agreed with our study in that the frequent NFC changes in DM include; enlargement of capillaries, branched capillaries, capillary loss (avascular areas) and capillaries hemorrhage. **Manfredi *et al.*** [2] added disarray of vascular architecture. Reviewing other studies, scleroderma like pattern varied significantly from 27% to 100% in patients with PM and DM [15]. We can conclude that different percentages of scleroderma like pattern can be explained by various scleroderma like pattern definitions.

The current study failed to document statistically significant relationship between NFC findings and duration of the disease. Although association of severe NFC changes tend to occur early (<6 months disease duration) rather than late disease (>6 months disease duration), such as; giant capillaries (66.6% vs 28%), branched capillaries (50% vs 21%), and disorganized capillaries (50% vs 28.6%). In patients with DM and PM; shorter disease periods with incidence of more severe abnormalities, could be associated to the occurrence of more active disease which takes place mainly in the first months of the disease and decrease afterwards in response to improvement with treatment. The lack of association with disease duration could be attributed to the stability of the disease in most of patients.

These findings are consistent with that of **Mercer *et al.*** [15] who found that there were no statistically significant changes in the capillaries of patients with IIM and healthy controls over 6–12 months of their study. In contrast **Manfredi *et al.*** [2] found that DM patients who had less than six months disease duration (14/29 patients), their capillary density was markedly decreased (P=0.039) and had higher frequency of giant capillaries (P=0.027), in comparison to patients with longer disease duration, while a scleroderma like pattern had a tendency to occur more frequently in patients with less than six months disease duration. On the other hand, no difference was observed for branched capillaries regarding disease duration. Unexpectedly, shorter disease duration (early disease) was associated with more severe changes, while long-standing disease was linked to persistence of ramified capillaries.

In the current study we reported that; the global DAS was significantly higher in patients with branched capillaries, while there was no significant difference with other capillaroscopic parameters and skin activity score was significantly higher in patients with capillary hemorrhage. Different studies which focused on the relationship between NFC findings and disease activity, have been published showing conflicting results: **Shenavandeh and Nezhad** [21] stated that no significant relationship between disease activity indices and any of the NFC features. **Mercer *et al.*** [15] did not report an association between disease activity and capillary density in their study of DM patients. On the other hand, **Mugii *et al.*** [11] described a significant association between both muscle disease activity (p=0.01) and CK levels (p=0.01) and scleroderma capillary pattern in patients with DM. Moreover, they described a positive correlation between capillary loss and muscle disease activity (p=0.05) and global DAS (p=0.05), and between capillary hemorrhages and skin disease activity score (p=0.01). Overall, those results showed no or poor relationship between nailfold capillaroscopic changes and muscular affection in PM and DM patients, while there was a strong correlation with skin disease activity and skin manifestations. The hypothesis of the skin and muscle immune mediated injury in dermatomyositis may have different pathologic mechanisms, could explain the previous findings, however; there is not enough evidence to confirm these observations. Notably, muscle enzymes are not a sensitive disease activity index [22]. In our study also we found no correlation between NFC changes and CPK level.

A further point of concern is the possible association between NFC abnormalities and organ involvement, especially in interstitial pulmonary disease patients. The current study failed to document

a statistically significant difference between patients with or without interstitial lung disease as regard different capillaroscopic findings. However, a study done by **Selva-O'Callaghan *et al.* [17]** reported that interstitial pulmonary disease was related to high capillary scores. They confirm the fact that a common pathway underlies the abnormal NFC changes and interstitial pulmonary disease, whereas; nailfold capillaroscopic findings could be a valuable predictor of interstitial pulmonary disease in patients with IIM, providing the physician with the basis for suspecting this potentially serious condition.

CONCLUSION

Nailfold capillaroscopy is a simple, economic and non-invasive technique that may help the clinicians in diagnosis of DM and PM, it also allows for better characterization of disease activity and subtypes. DM and PM patients have active involvement of capillary vascular endothelium and a characteristic NFC pattern could be observed, which helps better characterization and classification of the disease. Capillary branching is more common in DM and PM patients with higher global DAS and capillary hemorrhage is more frequent in patients with higher skin activity score. More severe capillaroscopic changes are prominent in DM patients rather than PM and overlap syndrome patients. Further studies with greater numbers of patients and prospective studies would be beneficial to support our findings.

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