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ORIGINAL ARTICLE

The evaluation of nailfold capillaroscopy pattern in patients with fibromyalgia

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ABSTRACT

Objectives: This study aims to evaluate nailfold capillaroscopic pattern in patents with fibromyalgia and to assess the relation of capillaroscopic parameters with clinical variables and disease-related measures.

Patients and methods: This cross-sectional, case-control study included 60 participants (4 males, 56 females; mean age: 44.0±8.2 years; range, 26 to 64 years) between August 2019 and November 2019. All participants were divided into two groups as the primary fibromyalgia group (n=30) who met the 2016 modified American College of Rheumatology Diagnostic Criteria for Fibromyalgia and the control group (n=30) consisting of age- and sex-matched healthy individuals. Nailfold capillaroscopy was performed by a digital microscope under a magnification of 200×. Capillary density, capillary loop diameter, number of dilated, giant and neoangiogenic capillaries, capillary shape, number of avascular areas, micro-aneurysms and micro-hemorrhages were evaluated by an assessor who was blind to the group allocation. In the fibromyalgia group, Widespread Pain Index, Symptom Severity Scale scores, and Fibromyalgia Severity scores were calculated. Health status and presence of benign joint hypermobility syndrome (BJHS) were evaluated using the Fibromyalgia Impact Questionnaire (FIQ) and revised Brighton criteria, respectively.

Results: Of the capillaroscopic parameters, the mean capillary loop diameter, number of micro-aneurysms, avascular areas, and neoangiogenic capillaries were significantly higher in the patient group compared to the controls ($p<0.001$, $p=0.016$, $p=0.038$, and $p=0.04$, respectively). Nailfold capillaroscopic findings did not significantly differ between the patients with (n=16) and without concomitant BJHS (n=14). Of the disease-related measures, only FIQ score showed a weak correlation with the number of dilated capillaries ($p=0.324$).

Conclusion: Patients with fibromyalgia have distinct capillaroscopic patterns than healthy population. Capillaroscopic features, in general, are not related to clinical variables and disease-related measures.

Keywords: Capillaries, capillaroscopy, fibromyalgia, nailfold capillaroscopy.

Fibromyalgia is a chronic rheumatic condition affecting a large proportion of individuals worldwide. A survey conducted in five European countries demonstrated the estimated point prevalence as ranging from 2.9% to 4.7%, depending on the screening questionnaire used.[1] However, much higher rates were reported in patients with inflammatory rheumatic conditions, such as rheumatoid arthritis and spondyloarthritis.[2-4] Despite its high recognition among physicians, there are still unsolved points in terms of the etiology and pathogenesis of the disease. For a better understanding of the disease etiopathogenesis, clinical picture of the disease and each individual symptom/sign should be examined thoroughly.

Fibromyalgia has a wide range of clinical symptoms including chronic widespread pain,

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fatigue, unrefreshed waking, cognitive problems, headache, abdominal pain/cramps, and mood disorders.[5] Vasospastic symptoms are also common in patients with fibromyalgia.[6] Besides, pain -the cardinal symptom of fibromyalgia- may be related to muscle hypoperfusion induced by regional vasomotor dysregulation.[7] In this context, a number of studies have focused on the microcirculation abnormalities in patients with fibromyalgia, showing diminished microcirculation in fibromyalgia.[6,8-10] However, there is a limited number of studies using distinct methodologies. Besides, evidence regarding the potential relation between disease severity and microcirculatory abnormalities remains limited.

Given this gap in the literature, the primary objective of the current study was to evaluate nailfold capillary morphology in patients with fibromyalgia. Secondary objectives were *(i)* to examine the relationship between capillaroscopic findings and disease-related variables (i.e., pain intensity, disease severity and current health status) and *(ii)* to identify the potential impact of concomitant joint hypermobility on capillaroscopic abnormalities.

PATIENTS AND METHODS

This cross-sectional, case-control study was conducted at Çukurova University Faculty of Medicine between August 2019 and November 2019. A total of 60 participants (4 males, 56 females; mean age: 44.0±8.2 years; range, 26 to 64 years) were included in the study. All participants were divided into two groups as the primary fibromyalgia group (n=30) who met the 2016 modified American College of Rheumatology (ACR) Diagnostic Criteria for Fibromyalgia[5] and the control group (n=30) consisting of age- and sex-matched healthy individuals. Exclusion criteria were as follows: having inflammatory rheumatic diseases, concomitant diseases with a potential risk for microvascular involvement, any known vasculopathy, and the use of vasodilatory medications. A written informed consent was obtained from each participant. The study protocol was approved by the Ethics Committee of Çukurova University Faculty of Medicine (approval date: 05/07/2019, no: 90/13). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Demographic variables including age and sex of each participant were recorded. In the patient group, disease duration (months), Widespread Pain Index (WPI), Symptom Severity Scale (SSS) scores, and Fibromyalgia Severity (FS) scores were also noted. The WPI and SSS scores were evaluated as described in the 2016 modified ACR diagnostic criteria. The FS scores were calculated as the sum of WPI and SSS scores.[5]

The patients' current health status was evaluated using the Fibromyalgia Impact Questionnaire (FIQ).[11,12] This self-administered tool consists of 10 items. The first item contains 11 questions measuring physical functioning on a 4-point Likert scale (0-3). The following two items ask the number of days (0-7) that the patient felt well (item 2) and was unable to work (item 3) due to fibromyalgia. The remaining seven items (item 4-10) rate work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression (0-10). The total FIQ score ranges between 0 and 100. Higher scores represent poor current health status. The patients were also evaluated in terms of joint hypermobility using the Beighton scoring system.[13] Diagnosis of benign joint hypermobility syndrome (BJHS) was made based on the revised Brighton criteria.[14]

Nailfold capillaroscopy was performed using a digital microscope (Dino-Lite CapillaryScope 200, Naarden, Netherlands) and related software program (The DinoCapture v2.0 software from AnMo Electronics Corp., Taiwan). The methodology was adopted and modified from the previously published studies by Hosking et al.[15] and Sulli et al.[16] The procedure was performed by a certified physician who was blinded to the study groups. Prior to the procedure, the participants rested for 15 to 20 min in a temperature-stable outpatient clinic room. Immersion oil was applied to the nailfold epidermis of the second-fifth digits of both hands. Each nailfold was evaluated under a magnification of 200×, divided into four consecutive 1-mm fields and related images were recorded (Figure 1). Following parameters were evaluated on each field: *(i)* capillary density/number, *(ii)* capillary loop diameter, *(iii)* dilated capillaries,

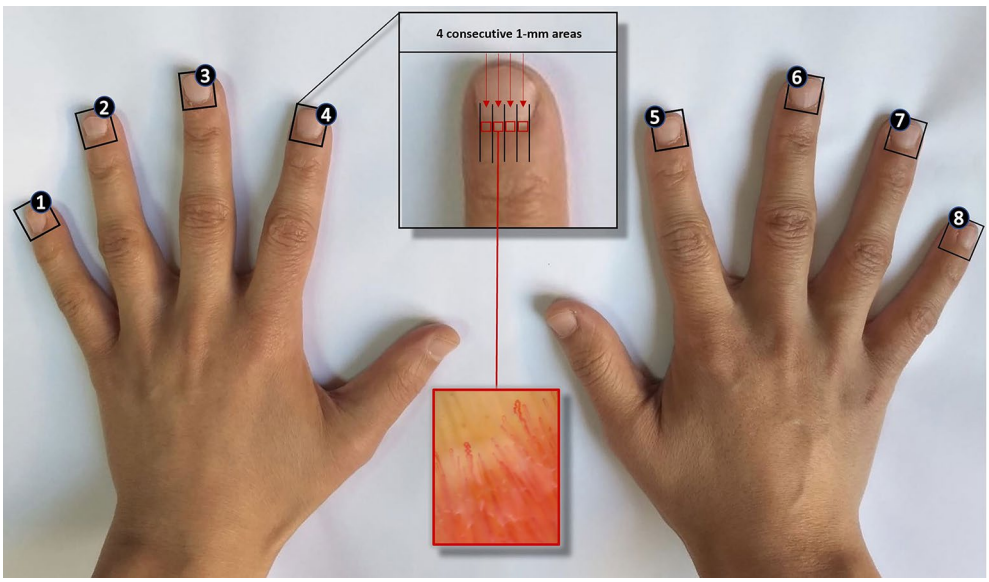

Figure 1. Methodology of nailfold capillaroscopy.

(iv) giant capillaries, *(v)* neoangiogenic capillaries, *(vi)* micro-hemorrhages, *(vii)* avascular areas, *(viii)* micro-aneurysms, and *(ix)* the dominant capillary shape. The number or presence of each capillaroscopic parameter was recorded on a standardized form. The total value of each parameter was calculated from the results of four consecutive fields on each digit. As for the capillary density and capillary loop diameter, a mean score value was obtained from all eight digits. As for the remaining capillaroscopic parameters including dilated capillaries, giant capillaries, neoangiogenic capillaries, micro-hemorrhages, avascular areas, and micro-aneurysms, the total number of each variable was calculated from eight digits. Capillaries with a diameter greater than >20 µm and >50 µm were defined as dilated and giant capillary, respectively. Distinct areas where two or more capillaries were missing in the nailfold were defined as avascular areas. An irregularly enlarged, circumscribed increase of the capillary loop diameter was considered micro-aneurysms. Dominant capillary shape was classified into three groups as normal, crossed, and tortuous.[15,17]

Statistical analysis

Power analysis and sample size calculation were performed using the G*Power version 3.1.0 software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). The effect size was based on the minimal statistically important difference in capillary diameter between patients and controls.[9] The alpha level and power were set as 5% (0.05) and 80%, respectively. Statistical analysis was performed using the IBM SPSS version. 20.0 software (IBM Corp, Armonk, NY, USA). The distribution of data was tested using the Shapiro-Wilk test and related histograms. Descriptive data were expressed in mean and standard deviation (SD), median (min-max), or number and frequency. Comparative analysis of normally-distributed continuous variables between fibromyalgia and control groups was performed by the independent samples t-test. Inter-group comparison of continuous variables with skewed distribution was done using the Mann-Whitney U test. The Fisher's exact test was used to compare categorical variables between the patient and control groups. The correlation of capillaroscopic parameters with clinical variables was analyzed using the Spearman's correlation analysis. A p value of <0.05 was considered statistically significant.

RESULTS

Demographic, clinical, and capillaroscopic characteristics of the study groups are shown in Table 1. Accordingly, the patients and control

Table 1. Demographic, clinical, and capillaroscopic characteristics of study groups (n=60)

	Control group (n=30)					Fibromyalgia group (n=30)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			43.5±9.0					44.5±7.5			0.631
Sex											0.305
Female	29	96.7				27	90				
Male	1	3.3				3	10				
FM-related parameters											
Disease duration (month)				-	-				36	5-120	-
WPI			-					12.7±3.3			-
SSS score			-					8.7±2.2			-
FS score			-					21.3±4.6			-
FIQ score			-					62.9±15.1			-
Capillaroscopic parameters											
Capillary density			9.3±0.9					9.0±1.1			0.375
Capillary loop diameter			8.5±1.0					10.1±1.0			<0.001
Dilated capillaries				0	0-3				0	0-6	0.138
Giant capillaries				0	0-0				0	0-1	0.317
Neoangiogenic capillaries				0	0-0				0	0-4	0.040
Micro-hemorrhages				0	0-0				0	0-3	0.078
Avascular areas				0	0-0				0	0-3	0.038
Micro-aneurysms				0	0-1				0	0-9	0.016
Dominant capillary shape											
Normal	26	86.7				26	86.7				>0.999
Crossed	4	13.3				4	13.3				
Tortuous	0	0				0	0				

SD: Standard deviation; Min: Minimum; Max: Maximum; FM: Fibromyalgia; WPI: Widespread Pain Index; SSS: Symptom Severity Scale; FS: Fibromyalgia Severity; FIQ: Fibromyalgia Impact Questionnaire.

groups were similar in terms of age and sex (p=0.631 and p=0.305, respectively). In the patient group, median disease duration was 36 (range, 5 to 120) months. The mean WPI, SSS, FS, and FIQ scores were 12.7±3.3, 8.7±2.2, 21.3±4.6, and 62.9±15.1, respectively.

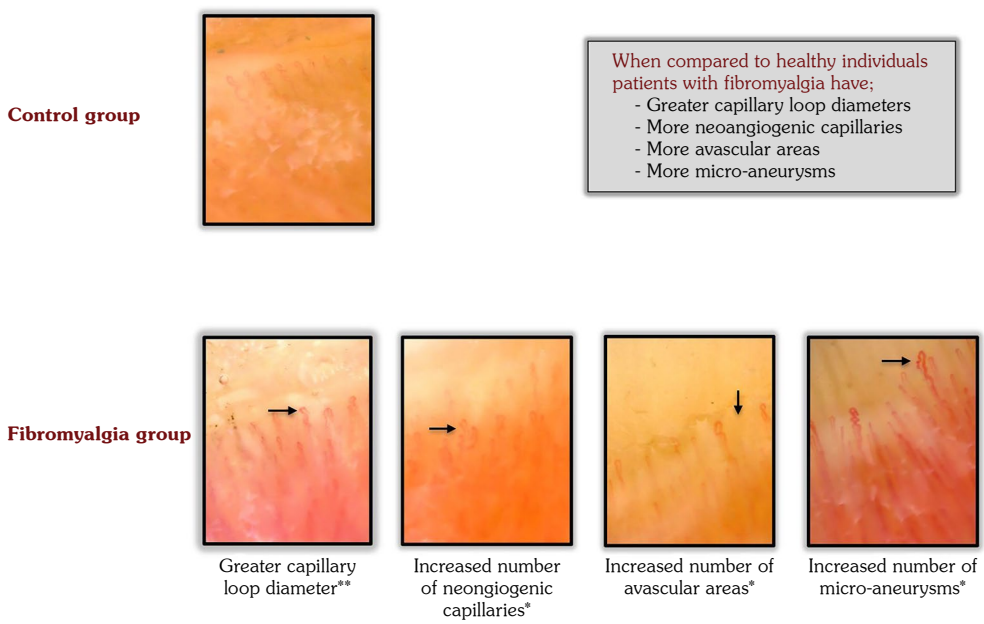

Figure 2. Comparison of capillaroscopic findings between patient and control groups.
* p<0.05; ** p<0.001.

Table 2. Correlation of capillaroscopic findings with disease-related parameters in patients with fibromyalgia (n=30)

Variables	Disease duration	WPI	SSS score	FS score	FIQ score
Capillary density	-0.121	0.219	-0.128	0.072	-0.195
Capillary loop diameter	0.174	-0.005	-0.035	-0.012	0.202
Dilated capillaries	0.146	0.156	0.038	0.142	0.371*
Giant capillaries	0.281	0.141	-0.195	0.000	0.161
Neoangiogenic capillaries	0.057	-0.100	-0.004	-0.062	0.068
Micro-hemorrhages	0.223	0.058	-0.156	-0.025	0.152
Avascular areas	-0.115	-0.107	-0.049	-0.101	0.007
Micro-aneurysms	-0.022	-0.261	-0.327	-0.279	-0.091

Values represent Spearman's rho; WPI: Widespread Pain Index; SSS: Symptom Severity Scale; FS: Fibromyalgia Severity; FIQ: Fibromyalgia Impact Questionnaire; * $p<0.05$.

The comparison of capillaroscopic parameters between the patients and controls is given in Table 1 and Figure 2. Accordingly, the mean capillary diameter was significantly greater in fibromyalgia patients than the controls (10.1±1.0 *vs.vs.* 8.5±1.0, respectively; $p<0.001$). However, the mean capillary density showed no statistically significant difference between the two groups ($p=0.375$). Numbers of micro-aneurysms, avascular areas, and neoangiogenic capillaries were significantly higher in the fibromyalgia group than the control group ($p=0.016$, $p=0.038$, and $p=0.04$, respectively). On the other hand, the number/presence of dilated capillaries, giant capillaries, and micro-hemorrhages did not significantly differ between the patients and controls ($p=0.138$, $p=0.317$, and $p=0.078$, respectively). In terms of dominant capillary shape, there was no significant difference between the groups. The results of the subgroup analysis in patients with fibromyalgia revealed that fibromyalgia patients with concomitant BJHS (n=16) and those without BJHS (n=14) had similar capillaroscopic findings.

The results of the correlation analysis of capillaroscopic findings with disease-related parameters are presented in Table 2. Accordingly, the number of dilated capillaries showed a weak correlation with the FIQ score ($r_s=0.371$, $p=0.044$). Other capillaroscopic measures were not correlated with disease-related variables.

DISCUSSION

The present study revealed that patients with fibromyalgia had morphologic abnormalities in microcirculatory system, including the increased capillary diameter and increased number of micro-aneurysms, avascular areas, and neoangiogenic capillaries. Such microcirculatory morphology is common in autoimmune and/or inflammatory rheumatic conditions. Nevertheless, it would be regarded as an unexpected finding in fibromyalgia and would lead to several questions in terms of disease etiology and pathophysiology: Does fibromyalgia has autoimmune/inflammatory background? Are these microcirculatory abnormalities related to symptoms and/or symptom severity in fibromyalgia? Could they be potential targets for treatment?

The endothelium, the essential organ for the regulation of vascular morphology, vascular tone and trafficking of numerous blood-borne molecules, is composed of a single layer of endothelial cells. The endothelium responds to various signals including mechanical, thermal, and chemical stimuli. A direct/indirect increase in any of these stimuli facilitates endothelial cell activation which, in turn, leads to endothelial dysfunction and the phenotypical modulation of the microvascular structure. Chemical stimuli including local factors such as pro-inflammatory mediators are one of the main confounders of endothelial dysfunction.[18] Microvascular changes can occur as

a result of inflammatory/immune damage, which is triggered by the recruitment of inflammatory mediators and immune cells in the endothelial tissue. Cytotoxic T cells and anti-endothelial cell, anti-angiotensin II and anti-endothelin type-A receptor antibodies are the main factors involved in endothelial cell apoptosis and/or secretion of chemotactic mediators, such as monocyte chemoattractant protein-1, interleukin (IL)-1, IL-6 and IL-8.[19] Thus, the combination of immune and inflammatory dysregulation leads to endothelial dysfunction, apoptosis, and loss of capillaries. The findings of the current study may partly support the suggestion about the role of inflammatory/autoimmune pathways in fibromyalgia, as microvascular abnormalities show similarity with those observed in inflammatory/autoimmune rheumatic diseases. During the last couple of decades, researchers have focused on the potential role of inflammation in fibromyalgia etiopathogenesis.[20-23] Although inflammation is not directly related to fibromyalgia, the results of these studies do not ignore its potential effect in disease background.[24] Several cytokines such as IL-6 and IL-8 showed increased levels in patients with fibromyalgia.[21,25-27] The increased serum/cerebrospinal levels of these mediators have been linked to peripheral/central neuroinflammation in fibromyalgia. Such an increase may be also responsible for structural disorganization in microvascular tissue, which is preceded by endothelial activation and dysregulation.[18] In this context, the potential relationship between pro-inflammatory mediators and nailfold capillary abnormalities still remains to be studied thoroughly.

Nailfold capillaroscopic changes in fibromyalgia syndrome may be also explained through sympathetic dysregulation. Abnormal adrenergic receptor reactivity and inadequate release of vasoactive mediators/neuropeptides are potential drivers of microcirculatory abnormalities.[19] The role of adrenergic receptors in fibromyalgia pathogenesis has been widely studied. Adrenergic receptor polymorphisms, which may affect responses to adrenergic glands, have been demonstrated in patients with fibromyalgia.[28] On the other hand, neuropeptide levels (neuropeptide Y, substance P and corticotropin-releasing hormone) are also increased in fibromyalgia.[20,29] Overall, recurrent vasospasm may induce endothelial dysfunction and such microstructural changes observed in our study sample.

One potential explanation of microvasculopathy in fibromyalgia may be the increased peripheral accumulation of reactive oxygen radicals. Serum levels of oxidative stress markers are elevated, mitochondrial deoxyribonucleic acid content and coenzyme Q10 are decreased in patients with fibromyalgia.[30,31] These factors along with the reduced levels of anti-oxidant enzymes lead to an increase in free radicals and oxidative stress in fibromyalgia.[30] Besides, there is an interplay among oxidative stress, hypoxia, and inflammation.[32,33] Endothelial cell injury, induced by oxidative stress and inflammation, may explain some capillary abnormalities including increased number of avascular areas. On the other hand, capillary neoangiogenesis may occur as a result of hypoxia-induced neovascularization.

As a secondary objective, the present study evaluated the clinical relevance of these capillaroscopic findings. Capillaroscopic variables did not significantly differ between the patients with and without concomitant BJHS. Besides, fibromyalgia-related variables were not associated with capillaroscopic parameters, except for a weak linear correlation between health status and number of dilated capillaries. However, the mean FIQ score of the study population was 62.9, and 83.3% had FIQ score above the average cut off (>50). Due to this homogeneity, it is difficult to draw a firm conclusion about the correlation of health status with capillaroscopic findings.

In daily clinical practice, nailfold capillaroscopy is often used for the differentiation of primary Raynaud's phenomena from secondary Raynaud's phenomena. Capillaroscopic findings are accepted to be normal in primary Raynaud's phenomena, while capillaroscopic abnormalities are seen in scleroderma spectrum disorders. Several abnormalities may be also observed in other connective tissue diseases, such as systemic lupus erythematosus and antiphospholipid antibody syndrome.[34,35] Capillaroscopic abnormalities (i.e., dilated capillaries) can be also seen in psoriatic skin.[36] In the present study, none of the participants had inflammatory rheumatic

conditions and dermatological diseases which would interfere with the results.

Nonetheless, there are some limitations to this study. First, the number of males is too small in our study which precludes the generalization of the results to the entire fibromyalgia population. Second, although the present study provides us data on microvascular changes in fibromyalgia, the cross-sectional design does not allow us to clarify whether microvasculopathy is a consequence or a cause of fibromyalgia.

In conclusion, patients with fibromyalgia show nailfold capillaroscopic changes including increased capillary loop diameter, increased number of micro-aneurysms, avascular areas, and neoangiogenic capillaries. However, capillaroscopic findings, in general, are not related to clinical variables and disease-related measures. The potential role of microvasculopathy in disease pathogenesis and treatment should be further studied.

Declaration of conflicting interests

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