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Nailfold Capillaroscopy Findings in Diabetic Patients (A Pilot Cross-Sectional Study)

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Abstract

Background: Microcirculation is affected in diabetes mellitus and Microvascular abnormalities cause persistent diabetic complications. The aim of this study was nailfold capillaroscopic assessment to describe the pathological changes (morphological and structural) in capillary of a large series of patients with type 1 and 2 diabetes. Methods: A cross-sectional study was carried out in a Nailfold Capillaroscopy Center (Tehran-Iran) between 2011 and 2014. The study included 235 types 1, 2 diabetic patients. All patients underwent 10 nailfolds capillaroscopy examinations. Microvascular architecture, disturbances capillary distribution, capillary morphology, capillary density, efferent/afferent limb ratio, sub-papillary venular plexus, and morphological abnormalities were evaluated. Conclusions were stated as normalor scleroderma pattern. Results of patients' capillaroscopic images were recorded and analyzed quantitatively and qualitatively. P value < 0.05 was considered as statistical significance. Results: of all participants with mean age 59.91 ± 12.39, 183 cases (77.9%) were female and 52 (22.1%) were male. Tortuosity of capillaries was more often observed in our subjects (235 cases) followed by angiogenesis (171 cases). Normal and early scleroderma patterns were observed in 195 (83.0%) and 40 cases (17.0%). Based on P values, altered micro vascular architecture, capillary distribution and capillary morphology were more frequent in patients with scleroderma pattern in comparison to patients with normal pattern (P value < 0.05). Morphological abnormalities except from neo formation capillary and mega capillary were also significantly more common in patients with scleroderma pattern than patients in counterpart group (P value < 0.05). Conclusion: Nailfold capillaroscopy as a non-invasive, diagnostic and prognostic method may potentially affect on diabetes outcome and control.

Keywords

Diabetes, Nail Fold Capillaroscopy, Normal Pattern, Scleroderma Pattern

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1. Introduction

Type 1, 2 diabetes is a worldwide disease with high risk of morbidity and early mortality. Persistent diabetic complications are mainly due to early stage in the pathogenesis of angiopathy and endothelial dysfunction. Both macro and microvasculature are affected in this disease by altered capillary flow, permeability associated with basement membrane thickening and blood cell velocity. Vascular damage, finally leads to eventual capillary obliteration. Morphological and functional changes in capillary microscopy have been reported in relation to vascular reactivity after induced ischemia [1]-[3].

Some techniques like nailfold capillaroscopy, laser Doppler flowmetry, retinal vessel analysis and 24-hour ambulatory blood pressure monitoring (24-hr ABPM) detect cardiovascular system damage once Type 1 or 2 diabetes is well established [2].

Nailfold capillaroscopy (NC) is a non-invasive, easy to perform, painless, and sensitive technique for evaluating microvascular involvement, mainly in Raynaud's phenomenon (RP), systemic sclerosis and connective tissue patients [3]-[5]. Moreover, capillaroscopy is now applied to predict the risk of development of future visceral complications and digital ulcers in patients with systemic disease [6]. The evaluation of the capillaroscopic pattern is not based on a single parameter, but on the judgment of an overall pattern resulting from the combination of numerical and morphologic characteristics such as capillary diameter (width), capillary length, shape, distribution, mean capillary density, presence of avascular areas, haemorrhages, neoangiogenic capillaries [5] [7]. The nailfold capillary bed is accessible and revealing capillaries lie parallel to skin allowing the whole capillary loops to be visualized [2].

Several capillary alterations have been explained in diabetes with poor metabolic control. In previous studies correlation between the severities of microvasculature changes and metabolic control of diabetes has also been reported [2]-[4]. Despite all these findings, little data exist on the relationship between microvascular changes in capillaroscopy and type 1, 2 diabetes features. Earlier diagnosis of vascular pathology with Capillaroscopy as a reliable method could be crucial for the therapy of diabetic patients [3]. Therefore the aim of this work was a quantitative and qualitative nailfold capillaroscopic assessment to describe the morphological and structural changes in capillary of a large series of type 1, 2 diabetic subjects.

2. Methods and Materials

2.1. Patients

A cross-sectional, observational study of adolescent and adult with diabetes, aged 13 - 86 years old between October 2011 and October 2014 was carried out in Nailfold Capillaroscopy Center of Tehran Resalat Hospital, a private General Hospital in Tehran, Iran. The study included 240 patients suffering from diabetes based on their medical records and laboratory examinations for at least one year. Informed consent was obtained from each participant.

The inclusion criteria were patients with diabetes, without symptoms of diabetes decompensation or acute infection and with satisfactory clinical control. The exclusion criteria were any evidence of clinical cardiovascular and microvascular disease, vascular coexistent disorders, hypertension, hepatopathy, collagen vascular disease, skin diseases, smoking, infection, vascular effective drug use and missing data.

The study was approved by the Research and Ethics Committee of Tehran Resalat Hospital.

2.2. Nailfold Capillaroscopy

All patients underwent a nailfold capillaroscopy examination using a videocapillaroscope.

Videocap D1 (DS Medica, Sr1, Milano, Italy, 2011). The optical microscope was connected to a digital camera and computer.

Participants were studied in the morning between 9 - 12 am. We asked them to abstain from caffeine and smoking for 12 hours before the examination. The procedure was explained for patients. The patient was placed in a semi-supine position for 15 minutes in a comfortable ambient temperature of 22˚C to 25˚C with their hands at heart level.

As there may be a high variability in morphology in diabetic patients per nailfold, we evaluated every 10 nailfold in a patient. A drop of immersion oil was placed on the nail fold of finger to maximize the translucency.

For each image the following capillaroscopic parameters were assessed by an expert rheumatologist: Micro-

vascular architecture, capillary distribution (morphology together the numbers), capillary density (the total number of erythrocyte-perfused capillaries per square millimeter of skin), efferent/afferent limb ratio, sub-papillary venular plexus (define according to Wertheimer's criteria, modified by Terreri *et al.*), and morphological abnormalities (bushy capillaries, Raynaud loops, megacapillaries) [4] [8] [9].

Conclusions were stated as normal, non-specific morphological abnormalities, and scleroderma pattern.

Although the combination of microvascular alterations in the nailfold and major morphological parameters including giant capillaries, A decreased number of loops (<30 over 5 mm in the distal row of the nailfold), disorganization of the normal distribution of capillaries, budding (bushy) capillaries, the associated micro-haemorrhages when they start to collapse, the loss of capillaries with a decrease in their density (7 - 10 capillaries/mm as the mean reference value), the neo-vascularisation, and reduced blood flow were detected as early capillaroscopic changes [10]-[12], we categorized our subjects in 2 groups according to Cutolo *et al.* [13]-[15]:

- Patients with two or more definitely abnormal morphological parameters (at least in two nailfolds) assclerodema pattern group.
- Participants with homogeneous distribution of hairpin-shaped capillaries (comb-like structure), with a density of between 9 and 14 capillaries per mm or existence of just one abnormal parameter (non-specific morphological abnormalities) as normal capillaroscopic pattern.

Finally all gathered data were recorded and analyzed statistically.

2.3. Statistical Analyses

Capillaroscopic images from all patients were analyzed quantitatively and qualitatively using SPSS16.0. Data are presented as mean ± standard deviation for continuous variables and n% for categorical variables. Independent-samples T test and chi-square test was used to analyze the relationships between variables. With the proposed sample size of 240, the study had a power of 90%. P value < 0.05 was used as statistical significance.

3. Results

Among 240 enrolled subjects, 5 cases were ineligible due to poor quality of capillaroscopy images, smoking, infection and missing data. Of all participants with mean age 59.91 ± 12.39, 183 cases (77.9%) were female and 52 (22.1%) were male.

Normal and early scleroderma patterns were observed in 195 (83.0%) and 40 cases (17.0%), respectively.

Visibility of sub-papillary venular plexus in all cases was notable but micro vascular architecture in 27% of all patients was abnormal (**Table 1**). Moreover, tortuosity of capillaries was more often observed in our subjects (235 cases) followed by angiogenesis (171 cases). Morphological abnormalities in all subjects are reported in **Figure 1**.

Table 1. Capillaroscopic pattern in all participants.

Variables		Total = 235 N (%)
Micro vasculararchitecture	Normal	170 (71.9)
	Altred	65 (27.7)
Capillary distribution	Regular	230 (97.9)
	Non homogenous	5 (2.1)
Capillary morphology	Homogenous	231 (98.3)
	Non homogenous	4 (1.7)
Capillary density	Normal	231 (98.3)
	Reduced	4 (1.7)
Sub-papillary venular plexus	Visible	235 (100)
	Non visible	0
Efferent/Afferent limb ratio	Normal	233 (99.1)
	Increased	2 (0.9)

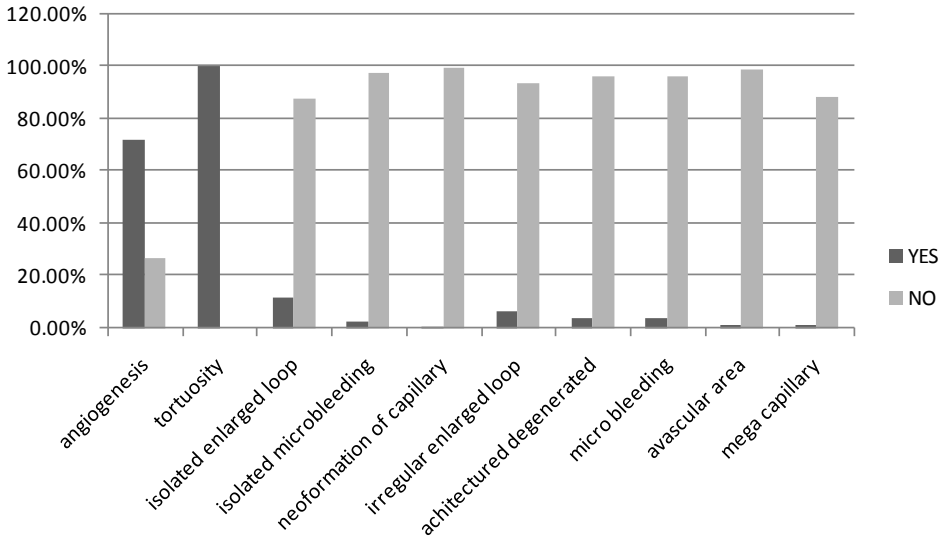

Figure 1. Morphological abnormalities in subjects.

Among 40 patients with scleroderma pattern, 33 of them were female. Tortuous capillaries, angiogenesis and altered micro vascular architecture were the most frequent morphological abnormalities in patients with scleroderma pattern. Based on P values, altered micro vascular architecture, capillary distribution and capillary morphology were more frequent in patients with scleroderma pattern in comparison to patients with normal pattern (P value < 0.05). Morphological abnormalities except from neo formation capillary and mega capillary were also significantly more common in these patients (with scleroderma pattern) than patients in counterpart group (P value < 0.05). Detailed data are demonstrated in **Table 2** and **Table 3**.

However, mean age in subjects with scleroderma pattern was higher than normal pattern (61 ± 8.81 vs. 59.69 ± 13 years), this difference was not statistically significant (P value = 0.543). No correlation was also found between different patterns (normal or scleroderma) and participants' gender (P value = 0.439).

Table 4 shows comparison of all micro vascular complications between men and women; statistical analysis showed no significant differences between both groups (P value > 0.05).

4. Discussion

We evaluated the frequency of nailfold capillaroscopic abnormalities of 235 patients with Type I and Type II diabetes mellitus and showed a high prevalence of pathological nailfold capillary changes.

According with our findings, morphological changes in diabetics' micro circulation were notable. This vascular heterogeneity may be related to significant autonomic neuropathy disturbances among population with this disease. Some other reports confirmed our results [2] [16].

In consistence to other investigations [3] [17], we saw a high frequency of capillary changes especially increased tortuosity of vascular loops and angiogenesis in diabetic patients. Kaminska-Winciorek *et al.* also showed an increased frequency of twisted capillaries in patients with diabetes type 1 and 2 [4]. Although we did not consider duration of disease, coiled capillaries were significantly reported in patients with diabetes with long-standing disease [18].

Of all participants 17% had different degrees of advanced microcirculation angiopathy (scleroderma pattern) that warned us for more attention against consequence complications.

In accordance with expectations, altered micro vascular architecture, capillary distribution and capillary morphology were seen more frequently in patients with scleroderma pattern in comparison to patients with normal pattern. We suppose that many factors like duration or severity of disease may be involved in micro circulation impairment. Barchettast *et al*. showed greater alterations of capillary length (P = 0.004), distribution (P = 0.02), and morphology (P = 0.0001) in their subjects with diabetes [18].

In addition, we saw that Avascular areas and micro bleeding were significantly more frequent in participants with scleroderma pattern. In consistent to our results Hosking *et al*. indicated more common Avascular areas and

Table 2. Comparison of capillaroscopic variables in patients with normal and scleroderma pattern.

Variables		Normal Pattern N = 195	Scleroderma Pattern N = 40	P Value
Micro vascular architecture	Normal Altered	153 (78.5) 41 (21)	16 (40) 24 (60)	**0.000**
Capillary distribution	Regular Non homogenous	195 (100) 0 (0)	35 (87.5) 5 (12.5)	**0.000**
Capillary morphology	Homogenous Non homogenous	195 (100) 0 (0)	36 (90) 4 (10)	**0.001**
Capillary density	Normal Reduced	193 (99) 2 (1)	38 (95) 2 (5)	0.135
Efferent/Afferent limbRatio	Normal Increased	194 (99.5) 1 (0.5)	39 (97.5) 1 (2.5)	0.312
Sex	Male Female	45 (23.1) 150 (76.9)	7 (17.5) 33 (82.5)	0.534

Table 3. Comparison of morphological abnormalities in patients with normal and scleroderma pattern.

Morphological Abnormalities		Normal Pattern N (%)	Scleroderma Pattern N (%)	P Value
Angiogenesis	Yes No	135 (69.2) 60 (30.8)	36 (90) 4 (10)	**0.006**
Tortuosity	Yes No	195 (100) 0	40 (100) 0 (0)	**0.000**
Isolated enlarged loop	Yes No	8 (4.1) 187 (95.9)	10 (47.5) 21 (52.5)	**0.000**
Isolated microbleeding	Yes No	1 (0.5) 194 (99.5)	4 (10) 36 (90)	**0.003**
Neo formation capillary	Yes No	1 (0.5) 194 (99.5)	0 (0) 40 (100)	.650
Irregular enlarged loop	Yes No	5 (2.6) 190 (97.4)	9 (22.5) 31 (77.5)	**0.000**
Architecture derangement	Yes No	3 (1.5) 192 (98.5)	4 (10) 36 (90)	**0.017**
Micro bleeding	Yes No	2 (1) 193 (99)	5 (12.5) 35 (87.5)	**0.002**
Avascular area	Yes No	0 (0) 195 (100)	2 (5) 38 (95)	**0.028**
Mega capillary	Yes No	1 (0.5) 194 (99.5)	0 (0) 40 (100)	0.650

Table 4. Comparison of micro vascular abnormalities between 2 genders.

Variables	Women (%)	Men (%)	P Value
Altered microvascular architecture	29	25	0.612
Non homogenous capillary distribution	2.7	0	0.228
Non homogenous capillary morphology	2.2	0	0.282
Reduced capillary density	2.2	0	0.449
Increased efferent afferent limb ratio	1.1	0	0.439
Angiogenesis	71	78.8	0.264
Toruosity	100	100	-
Isolated enlarged loop	12	9.6	0.631
Isolated microbleeding	2.2	1.9	0.908
Neo formation capillary	0.5	0	0.593
Irregular enlarged loop	7.1	1.9	0.164
Architecture derangement	3.8	0	0.152
Micro bleeding	3.3	1.9	0.612
Avascular area	1.1	0	0.449
Mega capillary	0.5	0	0.593

microhaemorrhages in participants with diabetes ($t = -2.33$, $P = 0.03$). They demonstrated a positive association between recent HbA1c and the number of microhaemorrhages ($r = 0.44$, $P = 0.03$) [2].

We also found that isolated and irregular enlarged loops were seen more frequently in cases with scleroderma pattern. Halfoun *et al*. highlighted the role of abnormal capillaries adaptation to hypoxia in prolonged vasodilatation and irregular loops enlargement among diabetic patients [19]. Meyer *et al*. have also shown capillary diameters of the apical part and the venous limb were enlarged in the combined analysis of type 1, 2 diabetic patients [20].

A higher frequency of enlarged capillaries and nodular apical elongation were reported in type 2 diabetic patients with chronic clinical complications by Pazos-Moura *et al.* [21], as well.

Despite of sub-papillary venous plexus visibility can be influenced by local conditions including hyperkeratosis, skin pigmentation, injuries and edema [5], this parameter was visible in all our subjects.

Ingegnoli *et al*. reported that reduced capillary density may be detected very early in patients with scleroderma pattern [5]; however, this finding was not consistent with our results. Meyer *et al*. also demonstrated tortuosity and dilatations but normal density of nailfold capillaries of subjects with type 1 diabetes [20].

We could not find any correlations between microvascular abnormalities and participants' age and sex. Kaminska-Winciorek *et al*. and Barchetta *et al*. depicted that microcirculation alterations revealed by nailfold capillaroscopy was independent from age and sex in patients affected by diabetes [4] [16].

The main strength of our study was demonstration of capability of nailfold capillaroscopy; a useful method for revealing diabetic microangiopathy. Besides that, such a large sample size study had not been previously carried out in Iran and our results can provide comparable data source to other publications.

5. Limitation

We did not evaluate relationships between altered parameters and duration or severity of disease. Some participants' para clinical data like blood sugar status, HbA1c level, … were not assessed, as well. Furthermore, in this project no control group was entered and studied. The answers to these questions definitely affect on our results interpretation.

6. Conclusion

Our results demonstrated that the presence of diabetes mellitus significantly influences on microcirculation mor-

phology and structure, which may predispose to occurrence of sever late complications. Moreover, nailfold capillaroscopy as a non-invasive and diagnostic method may potentially affect on diabetes outcomes and diabetic control.

Conflict of Interest

The authors declare that there is no conflict of interests.

Authors' Contributions

Dr. Rajaie carried out the design and coordinated the study, participated in most of the experiments. Dr. Dehghan coordinated and carried out all the experiments and participated in manuscript preparation, Mrs. Farahani was responsible for Analysis of data and manuscript review. All authors have read and approved the content of the manuscript.

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