Clinical Rheumatology (2020) 39:2671–2676
https://doi.org/10.1007/s10067-020-05025-3

ORIGINAL ARTICLE

Microangiopathy and forearm arterial blood flow in systemic sclerosis: a controlled study

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Received: 3 January 2020 / Revised: 26 February 2020 / Accepted: 28 February 2020 / Published online: 10 March 2020

Abstract

Objective The aim of the study was to evaluate the interrelationship between the micro- and macrovasculature.

Methods This is a cross-sectional study that examined SSc patients and fibromyalgia (FM) patients as controls. We assessed forearm peripheral vascular status and nailfold capillaroscopy. We evaluated the association between nailfold capillaroscopy pattern of microvasculopathy reflected as microangiopathy evolution score and macrovascular changes in the forearm vessels examined by color Doppler ultrasound. We assessed relevant clinical and laboratory data, as well as intima-media thickness (IMT) and internal diameter (ID) in the radial and ulnar arteries in millimeters, and calculated the ratio IMT\ID peak systolic velocity and end-diastolic velocity were used for the calculation of the resistance index.

Results We examined 73 patients: 50 patients with SSc and 23 patients with FM. Ten patients with SSc had arterial occlusions compared to 1 among FM patients ($p = 0.082$). The SSc group had a statistically significantly higher mean IMT to ID ratio ($p < 0.001$). There was no correlation between microangiopathy evolution score for both hands, RI, or mean IMT/ID ratio. Total microangiopathy evolution score was not associated with arterial occlusions.

Conclusions Our study demonstrated a high prevalence of macrovascular disease in SSc; no correlation was found between microvasculopathy and macrovascular disease, suggesting that different pathogenic mechanisms might operate in different vessels size.

Key Points
- *This study demonstrated a high prevalence of macrovascular arterial forearm disease in systemic sclerosis patients.*
- *This study found no correlation between capillaroscopic microangiopathy evolution score (MES) and macrovascular abnormalities.*
- *Our findings suggest that different pathogenic mechanisms might operate in different vessels size.*

Keywords Capillaroscopy · Color Doppler ultrasound · Macrovascular disease · Microangiopathy · Systemic sclerosis

Introduction

Systemic sclerosis (SSc) is a connective tissue disease that involves the micro- and macrovasculature and has noticeable immune and inflammatory changes that result in progressive tissue fibrosis. Several studies have investigated the pathogenic mechanism of this vascular involvement. Nailfold capillaroscopy (NFC) is a standardized method for the assessment of the microvasculature and is included in the ACR EULAR classification criteria of SSc [1, 2]. The microangiopathy evolution score (MES) is a composite score of capillary loss, disorganization of the microvascular array, and capillary ramifications; Sulli et al. first suggested it for assessment of microangiopathy in patients with SSc [3]. However, this score has not been assessed for its relevance in digital ulcers (DUs) or

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macrovascular damage in SSc. Noteworthy, studies about the association between NFC and macrovascular disease suggested that there might be a common pathogenic mechanism between micro- and macrovascular involvement [4].

In the present study, we evaluated the association between NFC pattern of microvasculopathy reflected as MES and macrovascular changes in the forearm vessels. The data were obtained by color Doppler ultrasound (CDUS) based on intima-media thickness (IMT), internal diameter (ID) IMT/ID ratio, and resistance index (RI) of the radial and ulnar arteries. Fibromyalgia (FM) patients without Raynaud's phenomenon were chosen as a control group because it is a non-inflammatory condition and age, sex, and comorbidities were expected to be simial to the study group.

Methods

This is a study on SSc patients and matched (for age and gender) fibromyalgia patients as controls for evaluation of forearm peripheral vascular status and NFC.

SSc and FM patients were recruited consecutively between October 2016 and June 2018. The patients had no specific indication for Doppler US. The study took place in two University Hospitals Rheumatology units: in the Ha'Emek Medical Center and Rambam Health Care Campus, Israel. Epidemiological and clinical data were retrieved from medical records.

Inclusion criteria were diagnosis of SSc according to the 2013 classification criteria for SSc [2] and diagnosis of FM according to the ACR classification criteria for FM [9], age above 18 years. Exclusion criteria were overlap with another autoimmune disease; pregnancy; participants in another investigational trial, peripheral catheterization and stent implantation in the brachial, radial, or ulnar arteries ever; and ethical contraindication to participate in the trial (i.e., inability to sign an informed consent form).

Patients data included age, gender, ethnicity, smoking, past medical history, comorbidities, and current drug use (Table 1). Each patient was evaluated for SSc signs: modified Rodnan skin score (mRSS), telangiectasia, calcinosis, active DUs defined as skin ulcer distal to PIP or IP joint either wet or crusted, past DUs defined as pitting scars and defined as skin scar distal to DIP joint, and sclerodactyly; relevant data on pulmonary hypertension and gastrointestinal involvement were extracted from the medical records. FM patients were examined physically for 18 tender points [5].

The US used was GE Logic E9 with a high frequency transducer (SL 15-4) in a B-mode imaging plan for arteries measurements and spectral Doppler plan for velocity measurements. All measurements were done by a radiologist or by the investigating rheumatologist trained for this purpose (a 3-h training session was performed in each center by all participants with a final assessment of dominant hand in three patients with SSc and three patients without SSc by each participant and comparison of results with 80% of compatibility).

IMT and the whole internal diameter (ID) in the radial and ulnar arteries in millimeters (mm) were measured, and the ratio IMT (mm)\ID (mm) was calculated.

Velocities and resistance index were measured at the wrist level in all patients and controls [8]. The peak systolic velocity (PSV) and end-diastolic velocity (EDV) were used for the calculation of the resistive index (RI): RI = (PSV-EDV)/PSV.

The microcirculation was evaluated by DinoLite CapillaryScope 200 MEDL4N/5 N 500 to magnify the view of the periungual area by approximately X230 times using immersion oil (Cargille Laboratories Immersion Oil CN 16482). The software used for picture analysis was DinoCapture 2.0 version 1.5.27A by the AnMo Electronics. Eight fingers were examined (fingers two to five for each hand), in a regular room air temperature of 23–25 °C. Patients were instructed not to perform any cosmetic procedures of manicure 4 weeks before the NFS. For each fingernail, two pictures of the central periungual part were taken and analyzed. The variables collected were the number of capillaries per 1 mm, the number of enlarged capillaries (loop width of 50–100 μm), giant loops (apical limb diameter of more than 100 μm), the number of micro-hemorrhages, area of capillary disorganization, and area of ramification. MES (a composite score of capillary density, capillary disorganization, and capillary ramification) was then calculated accordingly for each hand and the mean of both hands. Scoring is based on the number of capillaries (> 9 capillaries per mm = 0, 7–9 capillaries per mm = 1, 4–6 capillaries per mm = 2, < 3 capillaries per mm = 3); capillary disorganization which is the number of irregular distributed capillaries and orientation of capillaries, in respect to nailfold with shape heterogenicity (0 = 0% of capillaries, 1 = 0–33% of capillaries, 2 = 33–66% of capillaries 3= > 66% of capillaries); and capillary ramification such as branching, bushy, or coiled capillaries (0 = 0% of capillaries, 1 = 0–33% of capillaries, 2 = 33–66% of capillaries, 3= > 66% of capillaries). The NFC and MES scoring was performed by a trained rheumatologist (A.B) who underwent the EULAR capillaroscopy course in 2016 and is routinely practicing capillaroscopic studies.

Continuous data are presented as mean along with median and range. Categorical data are presented as number (%). In order to test group differences, chi-square or Fisher's exact test was used for categorical data, and the Wilcoxon 2 independent sample test was used for continuous data. Spearman correlations were performed to evaluate associations between the US measures (all patients and by group) and between the US measures and MES in the SSc group. Bonferroni-type correction was used to account for multiple testing. Significance was set at $p < 0.05$. All data analysis was performed using SPSS ver. 21.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Table 1 Demographic and basic clinical data of both groups

	FM ($n = 23$)	SSc ($n = 50$)	p value
Age	53.8 (52; 42–72)	54.6 (57; 21–77)	0.56
Gender			0.42
Female	22 (95.7%)	43 (86%)	
Male	1 (4.3%)	7 (14%)	
Ethnic group			0.09
Jewish	22 (95.7%)	38 (77.6%)	
Arab	1 (4.3%)	11 (22.4%)	
BMI	27.08 (25.71; 21.30–40.43)	25.36 (24.99; 18.18–36.50)	0.15
Current smoking	7 (30.4%)	7 (14%)	0.12
Disease duration (years)	5.6 (5; 1–20)	12.2 (10; 2–32)	0.001
Raynaud's phenomena	0 (0.0%)	49 (98%)	0.001
Hypertension per record	5 (21.7%)	4 (8%)	0.13
Systolic ≥ 140 and/or diastolic ≥ 90 at examination	3 (13%)	12 (24.5%)	0.36
Dyslipidemia	8 (35%)	11 (22%)	0.248
Statin use	4 (17%)	11 (22%)	0.701
Corticosteroids	2 (8.5%)	9 (18%)	0.448
Immunosuppressants	1 (4.5%)	15 (30%)	0.02
Anti-aggregates	5 (22%)	21 (42%)	0.09
Anti-coagulation	0 (0%)	6 (12%)	0.08
Oxygen saturation (%)	97% (97; 95–98)	97.50% (97; 93–100)	0.13
Modified Rodnan skin score	0 (0; 0–0)	4.14 (3; 0–22)	0.001
Gastric esophageal reflux disease	4 (17.4%)	48 (96%)	< 0.001
Estimated pulmonary hypertension measured by echocardiograph as PAP > 30 mmHg*	0 (0%)	16 (33.3%)	0.002
Hemoglobin (mg/dl)	13.2 (12.9; 12.0–15.0)	12.4 (12.4; 7.3–15.6)	0.009
Diabetes mellitus	4 (17.4%)	8 (16%)	0.88
ANA positivity > 1:160	2 (9.1)	42 (89.4)	< 0.001
CRP (mg/L)	4.23 (3.25; 0.30–14.0)	8.26 (3.60; 0.02–100.0)	0.82
Anti SCL70	0/20 (0%)	12/48 (25%)	0.01
Anti RNA polymerase 3	0/20 (0%)	3/49 (6%)	0.55
Anti-centromere	0/21 (0%)	16/48 (33%)	0.002
DU's	0 (0%)	15 (30%)	0.003
Periungual erythema	0 (0%)	28 (57.1%)	< 0.001
Past digital ulcers or/and pitting scars**	0 (0%)	41 (82%)	< 0.001
Sclerodactyly	0 (0%)	41 (82%)	< 0.001
Use of vasodilators***	3/30 (10%)	30/50 (60%)	0.003

**PAP* pulmonary artery pressure, **past digital ulcers per medical file record, ****vasodilators* use of calcium channel blockers or endothelin antagonists or PDE5 inhibitors or prostacyclin agonists

N (mean; range) or (percent)

Results

Seventy-three patients were evaluated (65 female; mean age 54 years; range 21–77): 50 patients with SSc and 23 patients with FM. Table 1 presents the demographic and selected clinical data; there were no statistically significant demographic differences between the groups. The SSc group had a statistically significant greater percentage with active DUs. Ten patients with SSc had ulnar arterial occlusions (either uni- or bilateral) compared to 1 among FM patients ($p = 0.082$). There were 3 patients with unilateral left ulnar artery occlusion (all in the SSc group), 4 patients with unilateral right ulnar artery occlusion (7 in the SSc group and 1 in the FM group), and 4 with both arteries occluded (all in the SSc group). There was no difference in smoking habits between groups.

Table 2 presents the radial and ulnar US and DUs findings. IMT to ID ratio was measured only in one center, and data is available for 20 FM patients and 38 SSc patients. The SSc group had a statistically significant higher mean IMT to ID ratio ($p < 0.001$) and a trend for lower mean RI though they did not reach statistical significance ($p < 0.07$).

Table 3 presents the MES data; patients with SSc had significantly higher left, right, and total MES ($p < 0.001$) compared with the control group.

No correlation was found between MES for both hands, RI, or mean IMT/ID ratio. There were no correlations between MES of the left hand or right hand separately and RI or mean IMT/ID ratio for each hand, respectively. Total MES was not associated with arterial occlusions. There was no correlation between MES score and a history of hypertension, diabetes, smoking, dyslipidemia, and BMI (Table 4). MES did not correlate with mean RI (adjusted R-sq = 0.053, $p > 0.21$). Similarly, same side MES was not associated with RI (adjusted R-sq = 0.043, $p > 0.38$; I (adjusted R-sq = 0.063, $p > 0.17$ for left and right, respectively).

There was no difference in total MES between patients with and without active DUs (4.85 ± 1.34 vs. 4.67 ± 1.34, p value = 0.72) or past DUs defined as digital pitting scars (4.86 ± 1.35 vs. 4.11 ± 1.11, p value 0.1).

Although not planned as an objective of this study, we found no difference in total MES between patients with and without pulmonary hypertension (assessed by echocardiography or right heart catheterization) (4.94 ± 1.18 vs. 4.66 ± 1.43, p value = 0.55).

However, there was a significant positive correlation between total MES and mRSS (Spearman correlation rho = 0.35, p = 0.014). Low mRSS scores for SSc patients in our study (mean 4.14) reflect skin involvement of mostly hands and fingers.

Table 3 MES score and NC phases between groups (score, ± confidence interval)

	Group		
	FM ($N = 23$)	SSc ($N = 50$)	p
MES			
Total	1.85 ± 0.75	4.72 ± 1.34	.001
Left	1.97 ± 0.79	4.72 ± 1.38	.001
Right	1.72 ± 0.77	4.76 ± 1.50	.001
Phase			
Active	0 (0.0)	6 (12.2)	.001
Early	0 (0.0)	1 (2.0)	
Late	0 (0.0)	37 (73.5)	
Normal	23 (100.0)	6 (12.2)	

MES microangiopathy evolution score

Discussion

Our study showed frequent ulnar artery occlusion in SSc patients compared with FM patients. This fact reflects a tendency to macrovascular disease in patients with SSc. Microvascular injury on NFC assessed by MES was often more severe in patients with SSc and was correlated with mRSS. MES did not show correlation with active or past DUs nor did it show correlation with indices of arterial assessment such as IMT/ID or RI. As expected IMT/ID ratio in SSc patients was elevated compared with controls. Luders et al. investigated the association between color Doppler ultrasound (CDUS) of digital, ulnar, and radial arteries measures; NFC patterns; and past or active DUs. The study suggested that digital and ulnar angiopathy is associated with DUs

Table 2 Ultrasound Doppler resistance index (RI) results mean ± standard deviation

	Group		
	FM ($N = 23$)	SSc ($N = 50$)	p value
RI			
Radial right	0.90 ± 0.15	0.87 ± 0.20	0.35
Ulnar right	0.82 ± 0.25	0.73 ± 0.35	0.4
Radial left	0.90 ± 0.13	0.86 ± 0.19	0.46
Ulnar left	0.93 ± 0.12	0.77 ± 0.37	0.18
Mean RI	0.89 ± 0.13	0.81 ± 0.19	0.07
RI (one/two) ulnar arteries = 0, (occluded arteries)	1 (4.3%)	10 (20%)	0.082
IMT/ID	$N = 20$	$N = 38$	
Radial right	0.16 ± 0.05	0.26 ± 0.27	0.08
Ulnar right	0.21 ± 0.08	0.42 ± 0.28	0.002
Radial left	0.18 ± 0.06	0.26 ± 0.14	0.04
Ulnar left	0.22 ± 0.09	0.41 ± 0.26	0.002
Mean	0.19 ± 0.05	0.33 ± 0.17	0.001

RI resistance index, *IMT* intima-media diameter, *ID* internal diameter

Table 4 MES score and correlation to classic cardiovascular risk factors

	MES total			MES left			MES right		
	Yes	No	*p*	Yes	No	*p*	Yes	No	p
Hypertension	3.63 ± 1.50	3.83 ± 1.84	0.76	3.86 ± 1.53	3.84 ± 1.82	0.97	3.45 ± 1.70	3.84 ± 1.97	0.57
Diabetes	3.45 ± 1.73	3.87 ± 1.80	0.47	3.28 ± 1.54	3.94 ± 1.81	0.26	3.60 ± 1.97	3.82 ± 1.90	0.73
Active smoker	3.42 ± 2.18	3.90 ± 1.69	0.38	3.54 ± 2.22	3.92 ± 1.66	0.48	3.30 ± 2.21	3.90 ± 1.86	0.29
Dyslipidemia	3.90 ± 1.84	3.70 ± 1.88	0.68	4.02 ± 1.84	3.65 ± 1.84	0.44	3.79 ± 1.92	3.76 ± 1.99	0.95

and disease severity. They also showed a correlation between advanced NFC patterns and occurrence of DUs and pitting scars [6]. As was pointed by Cutolo et al. in his editorial on Luders study, patients with a non-SSc-specific or early NC pattern tended to have a nonsignificant lower number of pathological arteries in CDUS than patients with active or late NC patterns [7].

As for macrovascular involvement, a review by Nussinovitch et al. summarized articles about macrovascular involvement in SSc [8]. It showed that flow-mediated vasodilation (FMD) was lower in SSc patients versus controls. In the same review, most IMT studies in SSc patients showed abnormal results (more than 0.9 mm). Hitherto, radial or ulnar IMT thickness was not evaluated in SSc patients. Another standard measure for an assessment of macrovascular disease is a resistive index (RI) and pulsatility index (PI). Rosato et al. found that patients with early NFC pattern had increased RI and PI and reduced peak systolic velocity (PSV) and end-diastolic velocity (EDV), reflecting a pathogenic correlation between microvascular and macrovascular involvement in SSc [9]. Frerix et al. found significantly decreased blood flow in ulnar and radial arteries in SSc patient that was correlated to the development of DUs [10]. Evaluating RI and NFC, Schioppo et al. had recently succeeded showing that both RI and low capillary density are correlated with a history of DUs [4]. Taking all that together, our study is the first to evaluate the correlation between MES as an integrated representative score for microvascular damage to DUs and radial or ulnar flow. In contrast to Rosato et al., we did not find this correlation, and it might be because of the integration of neovascularization into MES as opposed to measuring capillary density only.

Ulnar artery occlusion in SSc has been previously described and correlated with a higher risk of DUs and pitting scars [10]. Luders et al. did not found any correlation between NFC pattern (early, active, or late) and the presence of DUs or pitting scars [6], while other investigators and mainly the CAP study did show an increased risk of DUs with late pattern in capillaroscopy [11]. The majority of our SSc patients had late patterns (36 out of 50 patients); unfortunately this was not enough to power analysis for examining the association between phase pattern and DUs or pitting scars.

MES in our study correlated clinically only with mRSS but not with DUs, pitting scars, or pulmonary hypertension. So far, MES has been evaluated in a single study by Sulli et al. in which it progressed over time in the majority of patients, reflecting the evolution of the angiopathy in SSc [3]. In our study, as in Sulli et al.'s work, there have been no specific correlations between NFC scores and the majority of clinical parameters. In contrast, in our study, mRSS correlated with a worse MES. Our study is the first to examine the correlation between MES and macrovascular measures and found no correlation. This finding suggests that microangiopathy and macroangiopathy in SSc patients might not be present simultaneously in the same patient and have a different pathogenetic pathway.

Higher IMT/ID ratio in SSc patients compared with the control group in our study demonstrated that macrovascular involvement is very relevant in SSc. Mourad et al. previously reported higher IMT/ID ratios of radial arteries in patients suffering from Raynaud's phenomenon, although in their patients, the internal diameter was narrower and the IMT was not different compared with control, reflecting the vasomotor component of Raynaud's phenomenon [12]. Liu et al. measured IMT but not IMT/ID in 5 different locations including right radial artery; they did not find an increased IMT of the radial artery in SSc patients compared with controls [13].

Nussinovitch et al. summarized in their review five studies in which higher carotid IMT in SSc patients was demonstrated and seven studies demonstrating normal carotid IMT in SSc; however, these conflicting results did not address radial artery IMT/ID [8]. As previously reported, combining results of brachial flow-mediated vasodilatation and carotid IMT in SSc patient differ from classic atherosclerosis patients and do suggest that intimal or medial proliferation is a part of this disease pathogenesis [14, 15]. Another relevant trial examining IMT of the radial artery in the context of atherosclerosis found it to be a feasible imaging biomarker for atherosclerotic burden, using a 55 MHz transducer [16]. As shown in Table 1, in our study, classic atherosclerosis risk factors were not different between groups, although we did not evaluate these factors association with IMT/ID.

Our study has several limitations. As SSc is a rare disease, our SSc group included patients with relatively long disease

duration and prominent clinical manifestations. Of note, mRSS score is known to improve over time, and the results should be cautiously interpreted, meaning that MES and mRSS may correlate in long disease duration.

We could not control for multiple factors that might have confounded our results. Specifically, vasodilating agents such as calcium channel blockers, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors were used by patients with SSc, but the statistical analysis was not powered to control their influence. Yet, MES reflects changes that are of a long disease course and might not be directly influenced by those drugs.

Our control group was composed of FM patients and not "healthy" controls. We sampled only FM without any other autoimmune diseases and without evidence of Raynaud's phenomenon to minimize the chance of secondary FM. It is interesting to mention that MES was not "0" in the control FM group reflecting the range of normal and non-specific changes that one might encounter.

To conclude, our study demonstrated a high prevalence of macrovascular disease in SSc; we did not find correlation between microvasculopathy (according to MES) and macrovascular disease suggesting a different pathogenic mechanism between macro- and microcirculation in SSc. Previously reported outcomes about forearm arterial involvement in SSc were confirmed. Further studies about the correlation between the pathophysiological mechanisms of arterial injury in SSc (such as the role of endothelin, VEGF, and others) and the clinical outcomes such as DUs are needed.

Compliance with ethical standards

Conflict of interest Dr. Mader reports personal fees from Pfeizer, personal fees from Lilly, personal fees from AbbVie, personal fees from Novartis, personal fees from MSD, and personal fees from Sanofi, outside the submitted work. All other authors have no personal disclosures to declare.

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