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Microvascular involvement in Systemic Sclerosis and Systemic Lupus Erythematosus

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Abstract

Microvascular changes play central roles in the pathophysiology of systemic sclerosis (SSc) and systemic lupus erythematosus (SLE), and represent major causes of morbidity and mortality in these patients. Therefore, clinical tools that can assess the microvasculature are of great importance both at the time of diagnosis and follow up of these cases. These tools include capillaroscopy, laser imaging techniques, infrared thermography and iontophoresis. In this review, we examined the clinical manifestations and pathobiology of microvascular involvement in SSc and SLE as well as the methodologies used to evaluate the microvasculature.

Keywords

microvasculopathy; vasculitis; capillaroscopy; iontophoresis; laser; scleroderma; systemic lupus erythematosus

1. Background

Microvasculature is the part of the circulatory system composed of vessels <300 μm in diameter, including arterioles, capillaries, and venules.[1] Microvascular pathologies can manifest as vasculopathies or vasculitides. In general, vasculopathy refers to non-

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Author's contributions

DS participated in drafting the article and final approval of the manuscript submitted. KH and AT participated in design of the work, critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted.

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inflammatory vascular lesions, including those caused by immune complex deposition or intravascular thrombosis. On the other hand, vasculitis is characterized by leukocytic infiltration (polymorphonuclear or mononuclear) and fibrinoid changes of the vascular wall. Microvascular changes are the hallmarks of various connective tissue diseases, particularly systemic sclerosis (SSc) and systemic lupus erythematosus (SLE).

Scleroderma is a systemic autoimmune disease associated with the triad of vasculopathy, autoimmunity, and progressive fibrosis. The vascular involvement encompasses macro- and microvasculopathy. Macrovasculopathy is a relatively rare manifestation of SSc characterized by a more pronounced atherosclerosis due to alterations in the vascular wall. In contrast, microvasculopathy is responsible for the initial manifestations of SSc (e.g. Raynaud's phenomenon and nailfold capillary changes) and plays a central role in the development of digital ulcers, telangiectasias, pulmonary arterial hypertension (PAH), scleroderma renal crisis, gastric antral vascular ectasia and coronary microvascular disease. The degree and extension of microvascular involvement can guide physicians to early diagnosis of SSc, and provide valuable information about disease progression and prognosis.

Systemic lupus erythematosus is a complex, multi-organ autoimmune disease characterized by generation of autoantibodies, circulation of immune complexes, and activation of the complement system. Vascular involvement is considered the leading cause of death in patients with SLE, and presents with vasculopathic and/or vasculitic features. The vascular disease of SLE can affect all types of blood vessels from any site. Medium- and large-sized vessel disease include accelerated atherosclerosis, thrombosis associated with antiphospholipid syndrome and vasculitis of visceral, coronary and cerebral vessels. On the other hand, microvascular involvement can present as livedo reticularis, cutaneous vasculitis, lupus nephritis, pulmonary vasculitis, PAH, and intestinal vasculitis.

In SSc, microvascular changes are typically noticed in the form of vasculopathy. However, in SLE, features of both vasculitis and vasculopathy can be observed. We focus the present review on the microvascular changes seen in SSc and SLE. We describe the clinical manifestations, pathobiology and methodologies used to test the microcirculation, emphasizing their value in assessing disease severity and prognosis.

2. Clinical manifestations and pathologic findings of microvascular involvement in SSc and SLE

2.1 Cutaneous microvascular involvement

The skin is commonly involved in both SSc and SLE. The morphology of these skin lesions depends on the intensity of vascular injury as well as size and location of the involved vessels. Clinical manifestations include Raynaud's phenomenon, acrocyanosis, livedo reticularis, telangiectasia and cutaneous vasculitis.

Raynaud's phenomenon (RP) is a reversible discoloration of the digits triggered by cold exposure or emotional stress. It is found approximately in 90% of patients with SSc and 10–45% of subjects with SLE.[2,3] The pathobiology of RP includes endothelial dysfunction, abnormal adrenergic receptor reactivity and inadequate release of neuropeptides or

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vasoactive mediators [4] The recurrent episodes of vasospasm can lead to microinfarctions and the development of digital ulcers or less commonly gangrene of the distal portions of digits.

Another cutaneous microvascular involvement seen in both SSc and SLE is *acrocyanosis*. This condition is characterized by bluish discoloration and sweating of hands and feet upon cold exposure. While RP occurs episodically and may be associated with pain, acrocyanosis is characterized by a painless sustained discoloration with no initial phase of pallor. Microcirculatory dysregulation results in narrowed arterioles causing cyanosis and compensatory dilation of capillaries and post-capillary venules causing sweating.[5] Although acrocyanosis is less common than RP, the true incidence in SLE and SSc is unknown.

Livedo reticularis is also a cutaneous finding associated with microvascular involvement, found in 14–48% of patients with SLE. It manifests as a blanchable and purplish lace-like pattern predominantly located on lower extremities and aggravated by cold exposure. The underlying mechanism is spasm of dermal ascending arterioles with resultant swelling of cutaneous venules.[6]

In contrast to the aforementioned cutaneous manifestations, c*utaneous vasculitis* is an inflammatory microvascular disorder seen in 19–28% of patients with SLE and characterized by leukocytoclastic vasculitis with immune complex deposition involving the small vessels of dermis and/or subcutaneous tissue.[7] Depending on the severity of inflammation and the size and location of the vessels involved, cutaneous vasculitis may present as petechiae, palpable purpura, nodules, bullous lesion, urticarial plaque and/or cutaneous infarction.

RP and acrocyanosis are characterized by non-inflammatory vasculopathic changes that can be seen in patients with either SSc or SLE and aggravated by exposure to cold, suggesting a disruption in the thermoregulation of cutaneous vessels in both diseases (Table 1).

2.2 Pulmonary microvascular involvement

Pulmonary microvascular involvement includes PAH which is seen both in SSc and SLE, and pulmonary vasculitis which is particularly noted in patients with SLE (Table 1).

Pulmonary arterial hypertension is defined as a resting mean pulmonary artery pressure ≥ 25 mmHg with a pulmonary capillary wedge pressure ≤ 15 mmHg.[8] PAH is found in 8–12% of patients with SSc and is associated with severe Raynaud's phenomenon, more telangiectasias and decreased nailfold capillary density, conditions that indicate a systemic microvascular dysfunction.[9,10,11,12] PAH is less frequent in patients with SLE with a prevalence of 4.2%.[13] The mechanisms leading to the progressive remodeling of small- and medium-sized pulmonary arteries remain largely unknown. SSc- and SLE-associated PAH share the vascular features observed in idiopathic PAH including intimal hyperplasia, smooth muscle hypertrophy, medial thickening and the presence of plexiform lesions. In addition, SLE-associated PAH may also reveal pulmonary vasculitis and immune complex deposition in the affected vessels.

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Pulmonary vasculitis is a rare manifestation of SLE. In an autopsy study by Calamia et al., only 2 out of 120 cases were found to have true vasculitis.[14] This rare entity may present with alveolar hemorrhage secondary to capillaritis.

2.3 Renal microvascular involvement

Most SLE patients develop nephritis at some point during the natural course of the disease. However, in SSc, the renal involvement is less common, but critically important since it increases mortality (SSc renal crisis). In addition, there are a variety of subclinical renal lesions recognized both in SSc and SLE (Table 1).

Scleroderma renal crisis represents a life-threatening medical emergency, characterized by accelerated hypertension and acute renal failure, which can be accompanied by microangiopathic hemolysis in half of the cases. It is observed in 4–6% of SSc patients.[15,16] The pathobiology is poorly understood. Biopsy specimens show intimal thickening, myointimal cellular proliferation and glycoprotein and mucopolysaccharide accumulation in interlobular arterioles and small renal arteries, along with ischemic changes in glomeruli and tubules.

Renal microvascular involvement in SLE entails glomerulonephritis (lupus nephritis) and renal vascular lesions. *Lupus nephritis* is found in 50% of patients in the first year of diagnosis.[17] Six classes of lupus nephritis have been described, based on the severity and extent of the lesions (focal vs diffuse), light microscopy (proliferative, nonproliferative, inflammatory, or sclerotic), immunofluorescence and electron microscopy findings.[18] *Renal vascular lesions* are seen in 82% of patients with lupus nephritis and include vascular immune complex deposits, lupus vasculopathy, thrombotic microangiopathy and transmural necrotizing vasculitis.[19] These vascular lesions originate from endothelial injury in small renal arteries, arterioles and/or glomeruli due to cell-mediated injury, immune complex deposition and anti-endothelial antibodies.

2.4 Gastrointestinal microvascular involvement

Gastrointestinal microvascular involvement is recognized as a very rare manifestation of both SSc and SLE, and includes gastric antral vascular ectasia in patients with SSc and SLE, and intestinal vasculitis in SLE (Table 1).

The majority of gastrointestinal manifestations in SSc are thought to be due to a neural dysfunction that progresses to smooth muscle dysfunction, atrophy and fibrosis. However, g*astric antral vascular ectasia* is characterized by dilation of mucosal capillaries in the antrum of the stomach. It is found in 1–6 % of patients with SSc and less commonly in patients with SLE.[20,21] Clinical manifestations include anemia and upper gastrointestinal bleeding. *Intestinal vasculitis* is a life threatening condition seen in 0.2% of patients with SLE.[22] Histology reveals a small vessel arteritis and/or venulitis with inflammatory infiltration and fibrinoid necrosis in the vessel wall, thrombosis and immune complex deposition. Clinical presentation ranges from small ulceration to transmural infarction of the bowel.

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2.5 Coronary involvement

The coronary artery system is composed of epicardial arteries, pre-arterioles and arterioles. Accelerated atherosclerosis of large epicardial coronary arteries has been widely recognized in both SSc and SLE, independently of cardiovascular risk factors. On the other hand, patients with SLE and SSc frequently report symptoms of myocardial ischemia in the absence of an obstructive coronary artery disease that are due to coronary microvascular dysfunction (Table 1).[23] Coronary microvascular dysfunction is characterized by vasospasm followed by fixed structural alterations in small intramural coronary arteries and arterioles, contraction band necrosis and patchy myocardial fibrosis.[24] Coronary microvascular dysfunction can present with heart failure and/or arrhythmias, and is considered to be a poor prognostic factor.[25]

3. Pathophysiology of microvascular changes and biomarkers of vascular disease in SSc and SLE

3.1. Microvascular disease in SSc

Scleroderma microvascular disease is characterized by microvasculopathy, vasospasm, procoagulant state with thrombosis and fibrin deposition, and defective angiogenesis.

Microvasculopathy—Endothelial cell injury is thought to be the initial event in development of vascular disease in SSc. Factors involved in this injury include autoantibodies, infections (e.g. CMV), cytotoxic T cells, and reactive oxygen species. Autoantibodies include anti-endothelial cell (AECA), anti-angiotensin II receptor (ATRA) and anti-endothelin type-A receptor (ETRA) antibodies. AECA is found in 28–85% of patients with SSc and induce endothelial cell apoptosis and secretion of chemotactic mediators.[26,27,28] Clinically, AECA are associated with nailfold capillary abnormalities, digital infarcts and PAH.[27,28] On the other hand, ATRA and ETRA activate their respective receptors on endothelial cells, augment vasoconstriction and induce obliterative vasculopathy.[29] In fact, these autoantibodies have been shown to be associated with digital ulcers, PAH and higher mortality in patients with SSc (Table 2).[30]

Affected endothelial cells demonstrate endothelial cell activation with increased leukocyte adhesion molecules (e.g. E-selectin, vascular cell adhesion molecule -1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1)), cytoplasmic vacuolization, ballooning, cytoskeletal rearrangement, loosening of tight junctions and apoptotic changes.[31,32] Blood levels of endothelial cells detached from the affected vessels (i.e. circulating endothelial cells), soluble E-selectin, VCAM-1 and ICAM-1 are found to be elevated in patients with SSc and correlate with disease activity (Table 2).[33,34] Histologically, affected vessels are characterized by neointimal lesion (proliferation of endothelial and smooth muscle cells, and collagen deposition in intima layer), adventitial fibrosis, perivascular mononuclear cell infiltration, pericyte activation, distortion and loss of capillary loops in a variety of organ systems. The characteristic neointimal lesions likely result from an aberrant endothelial cell repair. Different cells may be responsible for generating neointimal lesions, including activated pericytes, adventitial cells, resident fibroblasts, vascular smooth muscle and endothelial cells (endo-mesenchymal transition).

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Vasospasm—Normal endothelial cells generate nitric oxide (NO) and endothelin-1 (ET-1) which contribute to the normal vascular tone. NO is a potent vasodilator, which inhibits platelet aggregation, smooth muscle cell proliferation and cytokine-induced endothelial activation. On the other hand, ET-1 is a vasoconstrictor that mediates smooth muscle cell proliferation, fibrosis and inflammation. In SSc, microvascular endothelial cells have decreased expression of endothelial NO-synthase with reduced NO and increased ET-1 production, leading to a vasoconstrictive state.[35] Elevated ET-1 levels were associated with higher systolic pulmonary artery pressure, more pronounced nailfold capillary changes and higher incidence of digital ulcers in patients with SSc (Table 2).[36]

Procoagulant state—A procoagulant state contributes to the vascular abnormalities in SSc. This state originates from the imbalance between coagulation and fibrinolysis, increased platelet activation and levels of pro-atherogenic oxidized LDL.[37,38] Patients with SSc have elevated levels of von Willebrand factor (vWF), fibrinogen, tissue plasminogen activator (tPA) and/or tPA inhibitor, resulting in microvascular thrombosis and fibrin deposition.[37] Of these factors, vWF was found to be associated with SSc severity and the presence of PAH (Table 2).[39] Oxidized-LDL is elevated in SSc and may promote endothelial dysfunction via generation of free radicals, impairment of NO-synthase expression and induction of pro-inflammatory genes.[40,41]

Defective angiogenesis—Chronic tissue hypoxia caused by microvasculopathy, vasoconstriction and microthrombosis triggers angiogenesis. However, angiogenesis is dysregulated in patients with SSc[42] This dysregulation results from the differential expression of proangiogenic (e.g. vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), fibroblast growth factor-2 (FGF-2)) and angiostatic (e.g. endostatin, soluble endoglin, CXC chemokine ligand- (CXCL) 4, 8, 9, 10) factors.[42,43] VEGF has been associated with decreased nailfold capillary density and the presence of PAH.[44,45] Endoglin was associated with telangiectasia and digital ulcers.[46] In addition, bone marrow derived circulating endothelial cell progenitors (CEPs) may affect angiogenesis since these progenitors replace the damaged endothelial in ischemic and injured tissues. Patients with SSc have lower number of CEPs when compared to healthy controls, particularly in patients with advanced disease.[47]

3.2. Microvascular disease in SLE

Microvascular abnormalities in SLE include vascular deposits of immune complexes, non-inflammatory necrotic vasculopathy, thrombotic microangiopathy and lupus vasculitis. SLE is characterized by polyclonal activation of B cells and generation of auto-reactive memory B cells that secret a variety of autoantibodies. These autoantibodies form immune complexes which tend to deposit at vascular bifurcations and small vessels, and activate endothelial cells via Fcγ receptors.

Anti-endothelial cell antibodies are present in more than 80% of patients with SLE and considered to be involved in the microvascular dysfunction of SLE.[48] These antibodies react with endothelial cell antigens like heparin-like compounds, heat shock protein-60, ribosome proteins, DNA, DNA-histone complexes, profilin II, plasminogen activator inhibitor,

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fibronectin and β2-glycoprotein.[49] Anti-endothelial cell antibodies activate endothelial cells with upregulation of leukocyte adhesion molecules (E-selectin, ICAM-1, VCAM-1 and endothelial leukocyte adhesion molecule-1), secretion of chemokines (monocyte chemoattractant protein-1 (MCM-1), interleukin 1, 6 and 8), and recruitment of leukocytes into the vascular wall. AECAs also cause endothelial cell injury via complement- and antibody-mediated cellular cytotoxicity. Serum levels of AECA were associated with cutaneous and digital vasculitis.[50] Serum anti-C1q, anti-interleukin 1 and anti-nucleosome antibodies, as well as IL-6, urinary soluble VCAM-1 and MCM-1 were associated with lupus nephritis (Table 3).[51]

Anti-phospholipid antibodies are present in 25% of patients with SLE and are related with arterial and/or venous thrombosis, development of PAH and recurrent fetal loss.[52] These antibodies react with negatively charged phospholipids (e.g. cardiolipin, diphosphate-glycerol, phosphatidylethanolamine, and phosphatidylethanolserine) that become exposed after endothelial injury, promoting thrombosis and exacerbating the initial injury. Finally, anti-neutrophil cytoplasmic antibodies (ANCA) are present in 15–20% of patients with SLE and associated with myocardial and renal involvements (Table 3).[53]

4. Methods to detect microvascular changes in SSc and SLE

A variety of methodologies have been developed to detect changes in the morphology and function of the microcirculation. Morphological changes can be assessed using capillaroscopy (nailfold and sublingual) and laser techniques (laser Doppler flowmetry and laser speckle contrast imaging). Functional changes with assessment of reactivity and dynamic function can be monitored with the same techniques by stimulating the capillaries with mechanical stimuli (post-occlusive hyperemia), thermal challenges (using local heating or cooling protocols) or iontophoresis of a number of medications (vasoactive agents are locally delivered to skin with the help of an electrical current).

4.1. Capillaroscopy

Capillaroscopy is a non-invasive tool that evaluates the morphology of capillaries using an optical magnification system. In patients with SSc, nailfold capillaroscopy (NC) abnormalities are referred as “scleroderma patterns” and are grouped in early, active or late forms of microangiopathy.[54,55,56,57] Early phase microangiopathy is characterized by a relatively well-preserved capillary architecture with a few dilated capillaries and microhemorrhages. Active pattern typically reveals mildly disorganized capillary architecture with many dilated capillaries and microhemorrhages along with avascular areas. Late pattern shows severely disorganized capillary architecture with dilated capillaries and microhemorrhages, but more importantly, a marked reduction in the number of capillary loops with large avascular areas.

Given its importance, NC findings were included in the 2013 American College of Rheumatology/European League against Rheumatism criteria for SSc diagnosis. Abnormal NC findings were found to be associated with the presence of PAH in patients with SSc, and correlated with PAH severity.[58] In fact, when compared to SSc patients without PAH, those with PAH had a more severe capillaroscopy pattern.[59] In addition, NC also helps

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differentiate healthy subjects from individuals with secondary Raynaud phenomenon (RP).[60] Healthy subjects and individuals with primary RP have normal capillaroscopy findings, whereas patients with secondary RP usually have pronounced abnormalities. Interestingly the discrimination between primary and secondary RP was improved, although not majorly, when NC was used in conjunction with laser doppler imaging and thermography.[60]

Newer technologies allow the study of other accessible vascular beds, i.e. periodontal and sublingual capillaries. These include orthogonal polarization spectral imaging, sidestream dark field imaging, and oblique profiled epi-illumination imaging. Periodontal capillaroscopy of SSc patients revealed reduced number of capillaries, and increased capillary diameter and tortuosity compared to healthy controls.[61] Similarly, sublingual microvascular assessment also showed reduced capillary density and perfusion in patients with SSc, in agreement with NC findings.[62] Further study of the microvasculature in SSc using these non-invasive tools may provide valuable information on which patients with SSc are more prone to develop PAH, thereby increasing the screening efforts in this subset of patients.[63]

Limited reports exist on the use of NC in SLE. [64,65] NC in SLE reveals non-specific morphological alterations including tortuous, corkscrew and bushy capillaries with associated hemorrhage. These findings have been seen in approximately 75% of SLE patients and shown to correlate with disease activity.[64] There are conflicting reports on the association between NC findings and organ involvement or RP in SLE.[64,65]

4.2. Laser techniques (laser Doppler flowmetry, laser Doppler imaging and laser speckle contrast imaging)

Laser techniques are non-invasive tools that assess skin capillary perfusion and include laser Doppler flowmetry, laser Doppler imaging, and laser speckle contrast imaging. These laser Doppler techniques assess the skin capillary perfusion by measuring the *Doppler shift* induced by laser light scattering of moving red blood cells. On the other hand, laser speckle contrast imaging (LSCI) measures the *fluctuating granular pattern* produced by laser light reflected on moving red blood cells. A comparison of different laser techniques is presented in table 4.

Studies comparing laser Doppler techniques and conventional NC showed that cutaneous perfusion measured by laser Doppler flowmetry correlated well with NC findings. [66,67] Moreover, microvascular response to cold stimulus measured by laser Doppler flowmetry was associated with disease progression by NC.[68] The advantage of laser Doppler techniques is that not only provide information about morphology but also on the dynamic behavior of microcirculation with different stimuli. This unique feature of laser Doppler techniques constitutes a promising approach and more studies need to be done to investigate its utility in clinical practice. One of the studies that was done by our group showed that patients with idiopathic PAH and SSc-PAH had lower blood flow index and greater vascular tortuosity in sublingual microcirculation compared to healthy controls by sublingual capillaroscopy, suggesting a systemic vascular dysfunction in both conditions.[69] Morphological clues detected with capillaroscopy in this study lead to another study done by our group which showed that patients with idiopathic PAH also had decreased vasodilatory

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response to treprostinil iontophoresis by laser Doppler flowmetry.[70] Therefore, we strongly believe that NC and laser Doppler techniques can be used together to complement each other in morphologic and functional evaluation of microcirculation and iontophoresis of vasoactive medications may be a promising tool in SSc-PAH to help to predict the response to specific PAH medications without associated systemic side effects.

Studies that explored the utility of laser Doppler flowmetry in SLE were less promising than those done in patients with SSc. For instance, the microvascular perfusion measured by laser Doppler flowmetry and its response to acetylcholine-iontophoresis were not different between patients with SLE and controls.[71,72] However, SLE patients with RP had an impaired vascular response to acetylcholine- and sodium nitroprusside-iontophoresis suggesting that SLE patients with RP have more pronounced microvasculatory involvement than those without RP.[72]

Lastly, laser speckle contrast imaging (LSCI) is a less time-consuming technique compared to NC and can be used to evaluate perfusion in the cutaneous microcirculation. Reports about LSCI are more limited compared to other laser techniques; however, LSCI showed lower perfusion in SSc patients than healthy controls and directly correlated with the NC findings seen in patients with SSc.[73,74] Also, it was shown to have very good inter-rater reliability in SSc patients.[75] However, more studies are needed for validation of LSCI in SSc. To our knowledge, no study has tested the utility of LSCI in patients with SLE.

4.3. Infrared thermography

Infrared thermography (IT) shows the body temperature distribution which can *indirectly* assess the cutaneous circulation. It captures the infrared radiation emitted from the body surface using digital thermal cameras and displays the finding as a visible information. This methodology has been investigated in patients with RP and SSc with digital ulcers. One study showed that hand thermography was very accurate at differentiating healthy controls from patients with RP; however, it might not be able to differentiate between primary and secondary RP.[60] In a retrospective study done on digital ulcer development in patients with SSc, hand thermography images were taken at 23 °C right after hands were immersed in 15 °C water and 30 °C in a climate-controlled room at the time of the SSc diagnosis. Authors showed that patients with abnormal initial thermography were more likely to develop digital ulcers and required more frequent surgical debridement.[76] To the time of this writing, no study has been done to evaluate the use of IT in patients with SLE.

5. Perspectives

Microvascular changes constitute a major cause of morbidity and mortality in patients with SSc and SLE. Therefore, clinical tools that assess the microvasculature are of great importance both at diagnosis and follow up. Several biomarkers have been associated with microvascular involvement in SSc and SLE. As we improve the understanding of the mechanisms behind the microvascular dysfunction in SSc and SLE, we will be able to refine the methodologies used to assess the microvasculature and translate them into clinical practice.

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List of abbreviations

SSc	Systemic sclerosis
SLE	Systemic lupus erythematosus
RP	Raynaud's phenomenon
PAH	Pulmonary arterial hypertension
AECA	Anti-endothelial cell antibody
ATRA	Anti-angiotensin II receptor antibody
ETRA	Anti-endothelin type-A receptor
VCAM-1	Vascular cell adhesion molecule -1
ICAM-1	Intercellular adhesion molecule-1
NO	Nitric oxide
ET-1	Endothelin-1
vWF	Von Willebrand factor
VEGF	Vascular endothelial growth factor
PDGF	Platelet derived growth factor
FGF-2	Fibroblast growth factor-2
CXCL	CXC chemokine ligand
CEPs	Circulating endothelial cell progenitors
NC	Nailfold capillaroscopy

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Table 1

Clinical manifestations of microvascular involvement in scleroderma and systemic lupus erythematosus.

	Scleroderma	**Systemic Lupus Erythematosus**
Cutaneous manifestations	Nailfold capilaroscopy changes Raynaud's phenomenon Acrocyanosis	Nailfold capilaroscopy changes Raynaud's phenomenon Acrocyanosis Livedo reticularis Cutaneous vasculitis
Pulmonary manifestations	Pulmonary arterial hypertension	Pulmonary arterial hypertension Pulmonary vasculitis
Renal manifestations	Scleroderma renal crisis Microalbuminuria with proteinuria Isolated reduced glomerular filtration rate Reduced renal functional reserve	Lupus nephritis Renal vascular lesions including immune complex deposits, lupus vasculopathy, thrombotic microangiopathy, transmural necrotizing vasculitis
Gastrointestinal manifestations	Gastric antral vascular ectasia	Gastric antral vascular ectasia Intestinal vasculitis
Coronary manifestations	SSc related myocardial disease	Coronary microvascular dysfunction of SLE

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Table 2

Potential biomarkers of microvascular involvement in SSc

Clinical manifestations	Candidate biomarkers
Nailfold capillary changes	Anti-endothelial cell antibodies (Serum) Endothelin-1 (Plasma) VEGF (Serum)
Digital ulcers, infarcts	Anti-endothelial cell antibodies (Serum) Anti AT1R, Anti-ETAR (Serum) Endothelin -1 (Plasma) Endoglin (Serum)
Pulmonary arterial hypertension	Anti-endothelial cell antibodies (Serum) VEGF (Serum) Endothelin -1 (Plasma) Von Willebrand factor (vWF) (Serum, plasma) Anti AT1R, Anti-ETAR (Serum) CXCL-4 (Plasma)
Scleroderma renal crisis	Anti-RNA polymerase I and III (Serum)

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Table 3

Potential biomarkers of microvascular involvement in SLE

Clinical manifestations	Candidate biomarkers
Digital and cutaneous vasculitis	Anti-endothelial cell antibodies
Pulmonary hypertension	Antiphospholipid antibodies
Lupus nephritis	Complement C4d (kidney biopsy, peripheral blood) IL-6 (serum) Anti-Interleukin 1 antibodies (serum) Anti-C1q antibodies (serum) Anti-neutrophilic cytoplasmic antibody (ANCA) (serum) Anti-nucleosome antibodies (serum) Monocyte chemoattractant protein-1 (MCP-1) (Urine) Vascular cell adhesion molecule-1 (VCAM-1) (urine) Neutrophil gelatinase associated lipocalin (NGAL) (urine) Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) (urine) Transferrin (urine) Ceruloplasmin (urine)

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Table 4

Comparison of characteristics of laser techniques.

	Laser Doppler Flowmetry	**Laser Doppler Imaging**	**Laser Speckle Contrast Imaging**
Speed	Fast at capturing changes in cutaneous perfusion	Slow at capturing changes in cutaneous perfusion	Fast at capturing changes in cutaneous perfusion
Reproducibility	Poor*	Good	Good
Skin contact	Needed	Not needed	Not needed
Area of assessment	Single point* ($\leq$1 mm^3)	Wide	Wide
Depth of skin penetration	1–1.5 mm		300 μm
Disadvantage	Regional heterogeneity of skin perfusion leads to high spatial variability	Not good at recording rapid changes in the perfusion	Not good for assessing areas of low perfusion, movement artifacts

*Integrated probes are available that provide better reproducibility and capture a larger area.