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Review

Vascular biomarkers and correlation with peripheral vasculopathy in systemic sclerosis

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ABSTRACT

Vascular disease is a hallmark of systemic sclerosis (SSc). It is present in every patient, being responsible both for the earliest clinical manifestations and the major life-threatening complications of the disease, and thus determining important morbidity and mortality.
In SSc, progressive vascular injury leads to vascular tone dysfunction and reduced capillary blood flow, with consequent tissue ischemia and chronic hypoxia. These phenomena are often accompanied by abnormal levels of vascular factors.
Microangiopathy in SSc may be easily assessed by nailfold videocapillaroscopy. The variety of derangements detected in the nailfold capillaries is accompanied by abnormal levels of different vascular mediators and appears to be the best evaluable predictor of the development of peripheral vascular complications, such as digital ulcers.
The purpose of this review is to summarize in SSc the most relevant vascular biomarkers and the main associations between vascular biomarkers and capillaroscopic parameters and/or the presence of digital ulcers.
Vascular biomarkers could become useful predictive factors of vascular damage in SSc, allowing an earlier management of vascular complications.

Contents

Abbreviations: AAVA, anti-annexin V antibodies; AECA, anti-endothelial cell antibodies; Ang, angiopoietin; ANGPTL, angiopoietin-like protein; AT_1R, antibodies against angiotensin II type 1 receptor; CCR, chemokine receptor; dcSSc, diffuse cutaneous systemic sclerosis; DcR, decoy receptor; DU, digital ulcers; ECs, endothelial cells; ECM, extracellular matrix; ENG, endoglin; ET, endothelin; ET_AR, entdothelin-1 type A receptor; EUSTAR, EULAR Scleroderma Trials And Research; IL, interleukin; JAMs, junctional adhesion molecules; MMPs, matrix metalloproteinases; NVC, nailfold videocapillaroscopy; PAH, pulmonary arterial hypertension; PBMCs, peripheral blood mononuclear cells; PDGF, platelet-derived growth factor; PlGF, placental growth factor; RBP, retinol binding protein; RP, Raynaud's phenomenon; sENG, soluble endoglin; sICAM, soluble intercellular adhesion molecule; SSc, systemic sclerosis; sVCAM, soluble vascular cell adhesion molecule; TGF-β, transforming growth factor-β; TWEAK, TNF-like weak inducer of apoptosis; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptors

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1. Introduction—systemic sclerosis is a vascular disease from its early onset

Systemic sclerosis (SSc; scleroderma) is a life-threatening connective tissue disorder of unknown etiology, characterized by widespread vascular injury and dysfunction, impaired angiogenesis, immune dysregulation and progressive fibrosis of the skin and numerous visceral organs [1–4].

A growing body of evidence supports the concept that SSc is primarily a vascular disease mediated by autoimmunity and evolving into tissue fibrosis [5,6]. The dysregulation of vascular tone control, clinically evident as Raynaud's phenomenon (RP), and microcirculatory abnormalities are the earliest clinical manifestations of SSc and may precede skin and visceral involvement by months or years [6–9]; the interval between RP onset and the first non-RP sign in SSc will predict the prognosis, as a short interval (weeks or months) is usually associated to a more aggressive disease course [10]. Telangiectasias, pitting scars, digital ulcers (DUs) and pulmonary arterial hypertension (PAH) may occur later in the disease process, severely affecting the quality of life of SSc patients [11].

In SSc, the progressive vascular injury is characterized by a persistent activation/damage and apoptosis of endothelial cells (ECs), intimal thickening and narrowing of the vessel which may evolve to lumen obliteration. Vascular remodeling leads to vascular tone dysfunction and reduced capillary blood flow, with consequent tissue ischemia and chronic hypoxia—a vicious cycle of ischemia–reperfusion injury, further exacerbated by extracellular matrix (ECM) accumulation due to fibrosis [4,9,10]. The whole process is characterized by an uncontrolled regeneration of the vasculature and subsequent microvascular loss, due to defects in both vascular repair and expected increase in new vessel growth (angiogenesis) [5,11]. The occurrence of overt vascular inflammation is less frequently observed [12].

In SSc, several studies have addressed the utility, in the clinical setting, of vascular biomarkers to evaluate the evolution of the pathological process affecting the vessels as well as to predict the outcome and the treatment response [13]. In this review, we focus the attention on the involvement of the microvasculature and present the main vascular biomarkers and their reported associations with the vascular features of the disease.

2. Peripheral vascular features of systemic sclerosis

2.1. Nailfold videocapillaroscopy: an open-window for detecting microvasculopathy in SSc

The damage of the microvessels evolves progressively from the early to the late stages in SSc, with different morphological abnormalities that are clearly shown by nailfold videocapillaroscopy (NVC) changes during the disease evolution [14–18]. These modifications are often accompanied by abnormal levels of angiogenic/angiostatic factors and markers of EC activation and injury.

The variety of NVC changes parallel the different degree of vascular disturbances in SSc [6,9]. In the early SSc, a pro-inflammatory state (giant capillaries) and an increased production of pro-angiogenic factors may stimulate angiogenesis (new abnormal and tortuous capillaries). This pro-angiogenic response is followed by a significant modification of the angiogenic process, which might in part be explained by the action of several angiostatic factors, ultimately resulting in a loss of angiogenesis characterized by a reduced capillary density and extensive avascular areas [9]. The most frequently observed NVC changes (giant capillaries, hemorrhages, avascular areas, ramified/bushy capillaries) are known as the "scleroderma pattern" [19]. According to their different proportions, they may distinguish an "early", an "active" and a "late" pattern of SSc capillaroscopy (Table 1) [20].

In SSc, NVC is a very useful clinical tool to achieve an early diagnosis, monitoring disease progression and predicting organ involvement [21–23]. The scleroderma pattern of nailfold capillary changes is used as a clinical diagnostic tool that enables physicians to distinguish patients with SSc from patients with uncomplicated primary RP [6]. High avascular scores were recently found to be an independent predictor of death in SSc [24] and patients with "late" NVC pattern had a higher frequency of pulmonary and esophageal involvement, compared to patients with the "early"/"active" patterns [25]. Therefore, the changes of the NVC pattern may represent a morphological reproduction of the evolution of SSc at microvascular level [20]. In RP patients, NVC can be used to monitor the modifications of the microcirculation thus establishing precisely the activity and severity of digital vascular disease [8].

2.2. Digital ulcers: an early consequence of vascular involvement

In SSc, DUs are an early manifestation of vasculopathy (vasomotor dysregulation and vascular histological changes) [10,26,27] and represent a considerable burden [28]. They are often extremely painful and cause significant impairment of hand function and activities of daily living, having a major impact on quality of life [28]. In SSc, DUs are frequent, averaging 30% prevalence according to the EULAR Scleroderma Trials And Research (EUSTAR) registry [29]. They result from ischemia due to vasospasm, intimal fibro-proliferation and thrombosis of the digital arteries; additional co-factors as sclerodactyly, calcinosis and local trauma may further contribute to their genesis [30]. The presence of persistent and severe DUs significantly increases the need for hospitalization of patients and for antibiotic treatment [31]. In addition, DUs are thought to be a clinical parameter of severe vasculopathy that can be associated with or predict other vascular lesions. Treatment of DUs remains challenging and the identification of reliable predictors of this complication is still an unmet clinical need in SSc [32].

3. Vascular biomarkers and correlations with NVC changes and DUs

Several vascular biomarkers have been studied in SSc and correlated with NVC changes and the presence of DUs (Table 2, Fig. 1).

3.1. Endothelial cell adhesion molecules

EC adhesion molecules play a pivotal role in angiogenesis, often acting in concert with angiogenic cytokines [33]. Adhesion molecules involved in cell–cell and cell–ECM interactions are important in the pathogenesis of the earlier stages of vascular alterations in SSc and have been suggested as potential biomarkers for SSc vasculopathy [1].

Table 1
"Early", "active" and "late" patterns of capillary microscopic changes in SSc [89].

	"Early" pattern	"Active" pattern	"Late" pattern
Architecture	Well preserved	Mildly disorganized	Disorganized
Focal missing of capillaries	+	++	+++
Avascular areas	−	−	+++
Hemorrhages	+	+++	(+)
Megacapillaries	+	+++	(+)
Elongated capillaries	+	++	+++
Ramified/bushy capillaries	−	+	+++

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