VASCULAR DYSFUNCTION AND SKIN FIBROSIS IN SYSTEMIC SCLEROSIS: PATHOGENETIC MECHANISMS AND THE ROLE OF TGF-B, PDGF, AND TSP-1

Hilola T. Mirakhmedova – D.M.Sc., professor
Bakhtigul I. Abdakimova – Ph.D. candidate
Tashkent State Medical University (Tashkent, Uzbekistan)
abdakimova.baxtigul@mail.ru

Abstract. *Background: Systemic sclerosis (SSc) is a heterogeneous autoimmune connective tissue disease characterized by microvascular abnormalities, immune dysregulation, and progressive fibrosis of the skin and internal organs. Vascular injury and fibrotic remodeling are closely interconnected, although the mechanisms linking these processes remain incompletely understood. Objective: To review the pathogenetic relationship between vascular dysfunction and skin fibrosis in SSc, with particular emphasis on transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), and thrombospondin-1 (TSP-1), and to discuss their potential clinical relevance. Methods: This narrative review is structured around established literature on SSc-associated vasculopathy, profibrotic signaling, and clinical assessment. The discussion integrates mechanistic reviews, relevant clinical guidance, and research on TGF-β activation and microvascular abnormalities. A systematic review methodology was not undertaken; therefore, this manuscript should not be interpreted as an exhaustive systematic review. Results: Available evidence supports a model in which endothelial injury, impaired vascular repair, immune activation, and fibroblast dysregulation contribute to the development of fibrosis. TGF-β is a central profibrotic mediator, whereas PDGF signaling supports fibroblast proliferation, migration, and tissue remodeling. TSP-1 may contribute to this process by activating latent TGF-β and modulating angiogenesis. Modified Rodnan Skin Score (mRSS) and nailfold capillaroscopy provide complementary clinical and microvascular assessments. However, the clinical and prognostic value of circulating TGF-β, PDGF, and TSP-1 requires direct validation in well-designed prospective cohorts. Conclusion: The interaction between vascular dysfunction and profibrotic signaling represents a relevant framework for investigating skin fibrosis in SSc. Combining serum biomarker measurements with standardized skin scoring and capillaroscopic assessment may help clarify disease mechanisms and identify potential prognostic markers.*

Keywords: *systemic sclerosis; skin fibrosis; vascular dysfunction; TGF-β; platelet-derived growth factor; thrombospondin-1; modified Rodnan Skin Score; nailfold capillaroscopy.*

INTRODUCTION.

Systemic sclerosis is a chronic autoimmune connective tissue disease characterized by variable combinations of vasculopathy, immune dysregulation, and fibrosis affecting the skin and internal organs. Its clinical course is heterogeneous, ranging from predominantly limited cutaneous involvement to rapidly progressive diffuse skin disease and severe visceral complications [1,2]. Vascular abnormalities are among the characteristic features of SSc. Endothelial dysfunction, structural microvascular damage, impaired angiogenesis, and abnormal vascular repair may contribute to tissue hypoxia and persistent cellular activation. At the same time, activated fibroblasts and excessive extracellular matrix deposition progressively alter tissue architecture and function [1,3].

Although vascular injury and fibrosis are often described as distinct pathological components, evidence suggests that they interact through multiple cellular and molecular pathways. Endothelial cells, immune cells, pericytes, and fibroblasts participate in a complex network of signaling mechanisms that may sustain both vascular damage and fibrotic remodeling [1,2].

Among the mediators implicated in these processes, transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), and thrombospondin-1 (TSP-1) are of particular interest.

TGF-β regulates extracellular matrix production and myofibroblast differentiation; PDGF signaling contributes to mesenchymal cell proliferation and migration; and TSP-1 can activate latent TGF-β while also influencing angiogenic processes [4–6].

The objective of this review is to examine the biological links between vascular dysfunction and skin fibrosis in SSc, focusing on these three mediators and discussing how they may be investigated alongside mRSS and nailfold capillaroscopy in future clinical research.

Vascular dysfunction in systemic sclerosis

2.1. Endothelial injury and microvascular remodeling The microvasculature is an important target of SSc-associated pathology. Endothelial dysfunction and structural vascular abnormalities can manifest clinically as Raynaud phenomenon, digital ischemic lesions, and characteristic nailfold capillaroscopic changes. Progressive capillary loss may coexist with attempts at vascular repair that fail to restore a normal microvascular network [1,3].

Impaired vascular homeostasis involves altered vasoactive signaling, abnormal endothelial-cell behavior, and an imbalance between proangiogenic and antiangiogenic influences. Persistent endothelial injury and defective vascular regeneration may contribute to tissue ischemia and the maintenance of pathological signaling between vascular and mesenchymal cells [1].

Nevertheless, vascular injury alone does not fully explain the development or distribution of fibrosis. The relationship between microangiopathy and fibrosis is influenced by disease duration, cutaneous subtype, immune activity, and other patient-specific factors. Vascular and fibrotic abnormalities should therefore be considered interacting but not necessarily temporally identical processes.

2.2. Interaction between vasculopathy and fibrosis Vascular dysfunction may contribute to fibrotic remodeling through several overlapping mechanisms. Tissue injury can alter local inflammatory signaling, while endothelial and stromal cells may release mediators that affect fibroblast activity. In turn, extracellular matrix accumulation and changes in the tissue microenvironment may further impair normal vascular organization. This reciprocal relationship provides a biological rationale for investigating vascular and fibrotic features together. However, the presence of an association between capillary abnormalities and skin thickening does not, by itself, establish that one directly causes the other. Longitudinal clinical studies and mechanistic investigations are needed to clarify temporal relationships and causality.

Profibrotic signaling pathways 3.1. Transforming growth factor-beta (TGF-β) TGF-β is a major regulator of fibrotic tissue remodeling. In susceptible tissues, its signaling can promote fibroblast activation, myofibroblast differentiation, and increased production of extracellular matrix proteins, including collagens. Persistent or dysregulated TGF-β signaling is implicated in the pathogenesis of SSc-associated fibrosis [4]. TGF-β activity is controlled not only by the amount of cytokine produced but also by its activation, receptor engagement, and downstream intracellular signaling. Consequently, the concentration of circulating TGF-β cannot automatically be assumed to represent the intensity of TGF-β signaling within fibrotic skin. TGF-β signaling may also intersect with pathways involved in vascular biology and cellular communication. These overlapping effects make it a biologically plausible candidate for research on the relationship between microvascular abnormalities and skin fibrosis. Nonetheless, its value as an individual circulating prognostic marker must be established empirically.

3.2. Platelet-derived growth factor (PDGF) PDGF signaling is involved in the regulation of mesenchymal cell proliferation, migration, and tissue remodeling. Through its receptors, PDGF can influence fibroblast behavior and contribute to the expansion or activation of cell populations involved in extracellular matrix deposition.

In the context of SSc, PDGF-related signaling is relevant to the broader network of profibrotic mechanisms that interact with TGF-β and other mediators [2,4]. The pathways should not, however, be regarded as interchangeable: they have overlapping biological effects but distinct receptors,

signaling mechanisms, and cellular functions. Measuring circulating PDGF may provide a potential research indicator of systemic biological activity. Interpretation requires careful consideration of the assay used and the possibility that sample collection and processing can influence measured concentrations. In particular, platelet activation during sample preparation may affect PDGF measurements, making standardized preanalytical procedures essential.

3.3. Thrombospondin-1 (TSP-1) Thrombospondin-1 is a multifunctional matricellular protein involved in cell–matrix interactions, vascular biology, and the regulation of latent TGF-β activation. Experimental research has demonstrated that TSP-1 can participate in the activation of latent TGF-β, providing a mechanistic link between extracellular matrix-associated signaling and profibrotic activity [5]. TSP-1 can also modulate angiogenic processes. Its biological effects depend on the cellular context, tissue environment, and interactions with other signaling molecules. Thus, TSP-1 may be relevant to both vascular dysfunction and fibrosis, but its role should not be simplified to a single, uniformly profibrotic effect in every setting. The hypothesis that circulating TSP-1 reflects the interaction between microvascular injury and skin fibrosis is therefore biologically plausible but remains to be tested in appropriately designed SSc cohorts. A correlation with mRSS or capillaroscopic severity, if observed, would require independent validation before clinical prognostic use could be recommended.

Clinical assessment of skin fibrosis and microvascular damage 4.1. Modified Rodnan Skin Score The modified Rodnan Skin Score is a standardized clinical method for assessing skin thickness in SSc. It involves palpation of 17 body areas, each graded on a scale from 0 to 3, producing a total score ranging from 0 to 51 [7]. The mRSS is widely used in clinical assessment and research because it provides a reproducible framework for describing the extent of cutaneous involvement and monitoring change over time. Its interpretation nevertheless depends on appropriate examiner training, standardized assessment, and consideration of disease stage and clinical subtype. In biomarker studies, mRSS can serve as a clinically meaningful outcome against which serum concentrations of TGF-β, PDGF, and TSP-1 are evaluated. Cross-sectional associations may identify relationships with current skin involvement, whereas repeated measurements are needed to examine whether baseline biomarker levels are associated with subsequent changes in skin score.

4.2. Nailfold capillaroscopy Nailfold capillaroscopy provides a non-invasive method for examining the microcirculation. In SSc, characteristic findings may include enlarged capillaries, microhemorrhages, reduced capillary density, and disorganization of the microvascular architecture. Recognized early, active, and late patterns describe different configurations of capillary abnormalities [3,8]. The 2024 British Society for Rheumatology guideline recommends assessment of nailfold microcirculation as part of the initial evaluation of SSc and when the disease is suspected [9]. Capillaroscopy therefore offers an established clinical framework for documenting microvascular abnormalities in studies investigating vascular and fibrotic processes. Combining capillaroscopic findings with mRSS may allow researchers to examine whether the severity of microvascular damage is associated with the extent of skin fibrosis. Standardized image acquisition, reporting criteria, and, where possible, blinded assessment can improve the reliability of such investigations.

Integrating TGF-β, PDGF, and TSP-1 with clinical measurements

The three mediators represent different but potentially interacting components of the vascular–fibrotic network. TGF-β is directly involved in extracellular matrix regulation; PDGF contributes to mesenchymal cell behavior; and TSP-1 may link extracellular matrix signaling, latent TGF-β activation, and angiogenic regulation [4–6]. A combined investigation may therefore provide more information than measurement of a single mediator. Nevertheless, biological plausibility should be distinguished from demonstrated diagnostic or prognostic performance. At present, the proposed combination should be treated as a research framework rather than an established clinical biomarker panel. Future studies should assess whether serum concentrations are associated with mRSS and

predefined capillaroscopic features. Analyses should account for relevant clinical factors, including cutaneous subtype, disease duration, age, treatment exposure, and other potential confounders. Assay selection, sample handling, storage conditions, and the distinction between total and biologically active TGF-β should be prespecified. Cross-sectional analysis can assess associations with current disease manifestations. To investigate prognosis, prospective follow-up is required, with predefined clinical outcomes and repeated measurements where feasible. A biomarker should not be described as prognostic solely because it correlates with disease severity at one time point.

Research gaps and future directions Several questions remain important for translating mechanistic knowledge into clinically useful biomarkers. First, circulating concentrations may not directly reflect activity within affected skin tissue. Second, the analytical properties of assays and preanalytical sample handling may influence results. Third, vascular abnormalities and skin fibrosis may change at different rates during the course of disease, complicating the interpretation of single-time-point measurements. A prospective study integrating serum TGF-β, PDGF, and TSP-1 with mRSS and standardized nailfold capillaroscopy could address these questions. The primary outcome should be defined before recruitment. For example, a study could examine the association between baseline biomarker levels and baseline mRSS, while a separate longitudinal outcome could assess change in mRSS over a prespecified follow-up period. The sample size should be determined using the primary outcome and a justified statistical assumption rather than convenience alone. Analytical validation, quality control, missing-data procedures, and a plan for handling multiple comparisons should be specified in advance. Independent validation would be needed before proposing a clinically useful prognostic model.

CONCLUSION.

Vascular dysfunction and skin fibrosis are interrelated components of systemic sclerosis pathogenesis. Endothelial injury, impaired microvascular repair, immune activation, and dysregulated profibrotic signaling contribute to a complex process of tissue remodeling. TGF-β, PDGF, and TSP-1 represent biologically relevant mediators for investigating the relationship between vascular pathology and fibrosis. Their potential clinical value may be explored through integration with mRSS and nailfold capillaroscopy. However, their performance as circulating diagnostic or prognostic biomarkers remains to be established through standardized, adequately powered, and preferably prospective clinical studies. A combined clinical and biomarker approach may improve understanding of SSc-associated skin fibrosis and provide a foundation for future validation studies.

REFERENCES

1. Affandi AJ, Radstake TRDJ, Marut W. Update on biomarkers in systemic sclerosis: tools for diagnosis and treatment. Seminars in Immunopathology. 2015;37:475–487. doi:10.1007/ s00281-015-0506-4.

2. Clements PJ, Lachenbruch PA, Seibold JR, et al. Skin thickness score in systemic sclerosis: an assessment of interobserver variability in 3 independent studies. The Journal of Rheumatology. 1993;20(11):1892–1896.

3. Cutolo M, Sulli A, Smith V. Assessing microvascular changes in systemic sclerosis diagnosis and management. Nature Reviews Rheumatology. 2010;6:578–587. doi:10.1038/ nrrheum.2010.104.

4. Denton CP, et al. The 2024 British Society for Rheumatology guideline for management of systemic sclerosis. Rheumatology. 2024;63(11):2956–2975. doi:10.1093/rheumatology/keae394.

5. Jinnin M. Mechanisms of skin fibrosis in systemic sclerosis. The Journal of Dermatology. 2010;37(1):11–25. doi:10.1111/j.1346-8138.2009.00738.x.

6. Lambova SN, Müller-Ladner U. Nailfold capillaroscopy in systemic sclerosis – state of the art: the evolving knowledge about capillaroscopic abnormalities in systemic sclerosis. Journal of Scleroderma and Related Disorders. 2019;4(3):200–211.

7. Murphy-Ullrich JE, Suto MJ. Thrombospondin-1 regulation of latent TGF-β activation: a therapeutic target for fibrotic disease. Matrix Biology. 2018;68–69:28–43. doi: 10.1016/j.matbio. 2017.12.009.

8. Trojanowska M. Cellular and molecular aspects of vascular dysfunction in systemic sclerosis. Nature Reviews Rheumatology. 2010;6:453–460. doi:10.1038/nrrheum.2010.102.

9. Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. The Journal of Clinical Investigation. 2007;117(3):557–567. doi:10.1172/JCI31139.