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Neurovascular Mediators and Psychological Symptoms in Systemic Sclerosis: A Cross-sectional Study

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Abstract:

Introduction: Recent research has demonstrated the role of vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) in both systemic sclerosis (SSc) and other neurological disorders. These molecules are central to neuroinflammation, synaptic plasticity, and neurovascular function, all of which are fundamental to the pathophysiology of these diseases. Given the apparent overlap, this study was designed to investigate the relationship between psychological symptoms and serum VEGF and MMP-9 levels in patients with systemic sclerosis (SSc).

Methods: This study employed a cross-sectional design and recruited patients with SSc. Serum levels of VEGF and MMP-9 were measured in the blood using certified immunoassays. Psychological symptoms were assessed using the Symptom Checklist-90-Revised (SCL-90-R). Correlation analysis was performed to examine associations between biomarker levels and psychological data obtained from the SCL-90-R. A mediation analysis was conducted to explore potential indirect relationships between biomarkers (VEGF, MMP-9) and psychological symptoms.

Results: Among 34 SSc patients (mean age 49.65 years), psychological distress was prevalent, with somatization and psychoticism showing the highest symptom scores on the SCL-90-R. VEGF and MMP-9 levels were within normal ranges but showed important associations: VEGF correlated with psychological symptoms, particularly paranoid ideation ($r = 0.6$, $p = .01$), while MMP-9 was linked to pulmonary artery pressure ($r = 0.4$, $p = .03$). Mediation analyses confirmed that VEGF significantly mediated the relationship between MMP-9 and multiple psychological domains.

Discussion: This study demonstrates significant psychological distress in SS patients and reveals meaningful associations between VEGF levels and psychological symptoms, even within clinically normal ranges, suggesting subclinical biomarker variations may contribute to emotional distress through neurovascular pathways. The findings align with existing literature while extending understanding by identifying VEGF as a mediator between matrix metalloproteinase-9 and psychological domains. However, the cross-sectional design limits causal interpretation, and the sample size was limited; therefore, findings should be interpreted with caution.

Conclusion: These results suggest that dysregulated VEGF and MMP-9, both crucial for vascular and fibrotic functions, can also influence or reflect psychological well-being in individuals with SSc. Further studies are needed to identify the psychobiological pathways involved. Thus, a more integrated, physiological–psychological health-based treatment strategy might improve clinical outcomes and quality of life for SSc patients.

Keywords: Scleroderma, Systemic sclerosis, MMP-9, VEGF, Psychological symptoms.

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1. INTRODUCTION

Systemic sclerosis (SSc), also known as scleroderma, is a chronic autoimmune condition that primarily affects connective tissue, resulting in widespread fibrosis and microvascular abnormalities in the skin and other organs [1]. The diseases typically affect the lungs, the gastrointestinal tract, the kidneys, and the heart, leading to high rates of mortality and morbidity. The effects of these physical manifestations–particularly visible facial and hand transformations – are psychosocially intense, often leading to body dissatisfaction, low self-esteem, and increased psychological distress [2]. Indeed, of the difficulties experienced by SSc patients, up to 14 per cent involve visible psychological distress, and 71.4% relate to social functioning [3]. These figures underscore the ramifications of SSc beyond somatic symptoms and highlight the need for a holistic approach to patient care that includes assessing and treating emotional health.

Psychological symptoms in chronic conditions like SSc are multifactorial. At one end, constant pain, functional limitations, and physical scarring often lead to emotional pain and social withdrawal [4]; at the other end, the unpredictable and progressive nature of the disease often causes anxiety and depression [5]. Such issues call for consideration not just because they impact wellbeing, but also because increasing evidence shows that mood disorders modulate inflammatory and immune functions that may contribute to the development of disease [6]. Understanding the psychobiological mechanisms of autoimmune conditions, therefore, remains a crucial clinical frontier.

Although its pathophysiology is not yet fully understood, angiogenesis, vasculogenesis, and extracellular matrix remodeling are believed to be central to the disease. Vascular endothelial growth factor (VEGF), a potent inducer of neovascularisation, is strongly associated with the vasculopathy characteristic of scleroderma, and elevated VEGF levels are thought to be related to lung involvement [7]. Apart from SSc, dysregulated VEGF regulation has also been linked to major depressive disorder (MDD) and schizophrenia (SCZ), making VEGF an interesting biomarker with potential application to both autoimmune and mental disorders [8]. Psychological stress may itself lead to increased VEGF expression through neuroendocrine and inflammatory pathways, suggesting a possible reverse causality in the observed association [9].

Similarly, matrix metalloproteinase-9 (MMP-9) has become well-known as an enzyme involved in tissue remodelling and fibrosis. Overexpression of MMP-9 in SSc can also trigger the fibrogenic remodeling characteristic of chronic skin and organ dysfunction [10]. In particular, elevated circulating MMP-9 levels have been associated with decreased hippocampal volume in SCZ, implying a relationship between neurostructural changes and MMP-9 function [11]. Similar correlations have been found in mood disorders, suggesting that MMP-9 could be a biomarker for depression [12].

Overall, these findings suggest that VEGF and MMP-9—proteins involved in blood vessel and tissue changes—may also be linked to psychological health in systemic sclerosis. However, the extent to which they influence or reflect the emotional impact of the disease remains unclear. This study aimed to regularly assess psychological symptoms in SSc patients and examine whether these symptoms are related to levels of VEGF and MMP-9 in the blood. By exploring these potential connections, we aim to gain a deeper understanding of how the body and mind interact in scleroderma, and ultimately support more comprehensive care for patients.

2. METHODS

This study adhered to the ethical principles of the Declaration of Helsinki. Approval was obtained from Shahid Beheshti University of Medical Sciences' ethical committee (IR.SBMU.RETECH.REC.1402.204). Informed consent was obtained from all individual participants included in the study. Individual data has been anonymized to protect confidentiality.

2.1. Participants and Clinical Examination

The cross-sectional study was conducted between May 2022 and August 2024 at Loghman Hakim Hospital, Tehran, Iran. A total of 34 patients with systemic sclerosis were recruited for the study. The inclusion criteria required participants to be at least 16 years old and have a diagnosis of systemic sclerosis, as defined by the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria [13]. Exclusion criteria included acute ischemic ulcers, renal failure, acute infections, serious comorbidities, or known central nervous system (CNS) disorders. Patients with a history suggestive of CNS conditions such as stroke, seizures, or neurodegenerative diseases were excluded following a thorough medical history and clinical evaluation.

2.2. Clinical and Demographic Data

We collected data on each participant, including age, gender, marital status, and educational level. Specific clinical features were also documented, such as the presence of limited or diffuse cutaneous scleroderma, history of digital ulcers, pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), and current medications. PAH was defined as a pulmonary arterial pressure (PAP) greater than 25 mmHg on transthoracic echocardiography. Additionally, chest CT scans were thoroughly reviewed for evidence of ILD.

2.3. Psychology Assessments

Participants' psychological status was assessed with the Symptom Checklist 90-Revised (SCL-90-R), a self-administered questionnaire. It measures nine major areas of psychopathology: somatization (SOM), obsessive–compulsive (OC), interpersonal sensitivity (IS), depression (DEP), anxiety (ANX), hostility (HOS), phobic anxiety (PHOB), paranoid ideation (PI), and psychoticism (PSY). All items are scored using a 5-point Likert scale from 0 ("very little") to 4 ("very bad"). T values above 60 are indicative of clinically significant distress or dysfunction, whereas scores below 60 tend to be more benign [14, 15].

2.4. Laboratory Measurements

Peripheral venous blood samples were drawn at the time of clinical assessment and appropriately stored for subsequent analysis. Serum levels of MMP-9 and VEGF were quantified using an enzyme-linked immunosorbent assay (ELISA), following the manufacturer's instructions (RK00217-96 and RK10102-96, respectively, Zellbio, Germany).

2.5. Statistical Analysis

To evaluate normal data distributions, the Kolmogorov –Smirnov test was applied. Pearson and Spearman correlation was applied to determine the correlation between biomarkers and psychological symptoms. A mediation analysis was conducted to explore potential indirect relationships between biomarkers (VEGF, MMP-9) and psychological symptoms. To mitigate the risk of Type I error arising from multiple comparisons, we applied the Benjamini-Hochberg (BH) correction. All statistical tests were calculated with a significance level of less than 0.05.

3. RESULTS

A total of 34 participants completed the study. Of these, 31(91.2%) were female and 3 (8.8%) were male. The mean age of the participants was 49.65 ± 9.48 years.

With regards to education 3(8.8%) were illiterate, 9(26.5%) had primary-level education, 17(50%) completed high school, and 5(14.7%) had an academic education. Several patients had concurrent illnesses, including 3 (8.8%) with diabetes, 10 (29.4%) with hypertension, and 9 (26.5%) with hypothyroidism. The mean duration of disease was 12.41 ± 8.83 years.

After clinical assessments, 18 patients (25.9%) were diagnosed with a history of digital ulcer, 27 (79.4%) with ILD, and 26 (76.5%) with pulmonary arterial hypertension. The mean PAP in the PAH subgroup was 30.79 ± 7.95 mmHg. In 22 (64.7%) patients, skin involvement was limited, and 11 (32.4%) patients had diffuse involvement (Table 1).

Table 1. Demographic and clinical characteristics of the sample.

Variables	Full Sample (N= 34)
Sex Male; n (%) Female; n (%)	 3(8.8) 31(91.2)
Age (years), mean ± SD	49.65±9.48
Disease duration (years), mean ± SD	12.41 ± 8.83
Marital; n (%) Married Single	 25(73.5) 9(26.5)
Level of Education; n (%) Illiterate Primary High school Academic	 3(8.8) 9(26.5) 17(50) 5(14.7)
Comorbidity; n (%) Diabetes Hypertension Hypothyroidism	 3(8.8) 10(29.4) 9(26.5)
Digital Ulcer; n (%)	18(52.9)
Interstitial lung disease; n (%)	27(79.4)
Pulmonary hypertension; n (%)	26(76.5)
PAP (mmHg) mean ± SD	30.79 ±7.95
Skin involvement; n (%) Limited Diffuse	 22(64.7) 11(32.4)
Biomarkers level; mean ± SD VEGF (pg/ml)	 949.17± 311.59
MMP-9(ng/L)	827.14 ±240.59

Table 2. Results of SCL-90 (mean ± SD).

Somatization	69.36 ±11.0
Obsessive-Compulsive	67.39 ± 8.8
Interpersonal Sensitivity	68.24 ± 8.65
Depression	66.51± 9.04
Anxiety	64.84 ± 8.49
Hostility	64.26 ± 6.57
Phobic Anxiety	64.27± 6.83
Paranoid Ideation	67.87 ± 8.27
Psychoticism	69.09 ± 6.42
Global Severity Index	67.79 ± 9.99
Positive Symptom Total	65.44 ± 7.46
Positive Symptom Distress Index	65.14 ± 8.81

Note: Scores ≥ 60 indicate clinically significant psychological distress.

In addition to the clinical and demographic parameters, the psychological condition of participants was evaluated using the SCL-90-R (Table 2). Overall, the scores indicate that participants experienced varying degrees of psychological distress. The patients achieved scores of 60 or higher on the SCL-90, and a T-score above 60 was a sign of dysfunction. Among the nine symptom dimensions, somatization and psychoticism demonstrated the highest mean score. The Global Severity Index (GSI), which reflects the

overall level of psychological distress, had a mean of 67.79 ± 9.99, indicating participants experienced a notable level of overall psychological distress, underscoring the need for mental health evaluation and potential intervention within this patient population. These results highlight the complex psychological load that scleroderma patients carry, from somatic issues to mood and anxiety states.

3.1. Correlation between VEGF and MMP-9 and Selected SCL-90-R Domains

Regarding biomarker levels, the mean serum VEGF level was 949.17 ± 311.59 pg/mL, and the mean serum MMP-9 level was 827.14 ± 240.59 ng/L, suggesting that both angiogenic and extracellular matrix remodeling pathways may be active in these patients. In our study, none of the participants had serum VEGF or MMP-9 levels exceeding the normal reference ranges defined by R&D Systems of Zellbio (VEGF: 78.1–5000 pg/mL; MMP-9: 31.2–2000 ng/mL).

Correlation analyses revealed a positive relationship between VEGF and certain psychological domains assessed by the SCL-90-R, including OC (r = 0.4, p = 0.005), IS (r = 0.4, p = 0.01), and PI (r = 0.6, p = 0.001). However, after applying the BH correction, only the correlation between VEGF and PI remained statistically significant (r=.06, p=.01). These results suggest that elevated VEGF levels might be related to certain aspects of scleroderma patients' psychological distress.

In contrast, MMP-9 levels did not demonstrate a significant correlation with any of the SCL-90-R domains, suggesting that although this biomarker may play a critical role in the fibrotic and inflammatory mechanisms of scleroderma, it may not directly predict the severity of symptoms on the tested psychological dimensions. Nevertheless, the observed positive correlation between VEGF and MMP-9 (r = 0.7, p = 0.001) underscores a shared or synergistic pathway that may exacerbate disease progression.

To investigate the proposed indirect relationship between MMP-9 and psychological symptoms through VEGF, we conducted a series of mediation analyses using the PROCESS Macro (Model 4, Hayes, 2022), controlling for age, gender, and disease duration.

Results consistently showed that MMP-9 significantly predicted VEGF levels across all models (*e.g.*, β = 0.88–0.95, p < .001). In turn, VEGF significantly predicted multiple psychological symptom domains, suggesting a mediating role in the MMP-9–psychological symptom relationship (Table **3**).

These results confirm the presence of significant indirect effects, supporting the hypothesis that VEGF mediates the association between MMP-9 and psychological distress in systemic sclerosis. They also highlight the relevance of neurovascular and inflammatory pathways in shaping emotional and cognitive outcomes in this population.

Furthermore, MMP-9 was positively correlated with PAP (r = 0.4, p = 0.03), suggesting that MMP-9 may be involved in the vascular complications of scleroderma. By contrast, VEGF did not correlate with PAP or any other clinical parameters, suggesting that its strongest associations were related to psychosocial, not cardiopulmonary, measures.

Table 3. Mediation analysis indicated that MMP-9 and psychological symptoms *via* VEGF.

Psychological Symptom Domain	Indirect Effect(95%CI)	Mediation Type
Somatization	.023(.005-0.053)	Partial
Obsessive-Compulsive	.018(.003-.057)	Full
Interpersonal Sensitivity	.016(.004-.039)	Full
Depression	.015(.004-.047)	Partial
Anxiety	.015(.003-.041)	Partial
Hostility	.013(.001-.040)	Partial
Phobic Anxiety	.013(.001-.028)	Full
Paranoid Ideation	.018(.005-.045)	Full
Psychoticism	.0009(.002-.027)	Potential full
Global Severity Index	.022(.006-0.052)	Potential full
Positive Symptom Total	.019(.005-.046)	Partial
Positive Symptom Distress Index	012(.003-.033)	Full

4. DISCUSSION

Its findings illuminate the complexity of SSc, the profound psychological distress of patients, and potential biological causes. A notably elevated GSI from the SCL-90-R confirmed that overall psychological symptom burden is high among participants, aligning with prior research suggesting that scleroderma's unpredictable course, visible disfigurement (especially of the face and hands), and chronic pain can adversely affect mental health. Previous studies have described a higher prevalence of depression and anxiety [16-18], as well as OC [16], in patients with scleroderma. These results, taken together, highlight the need for integrated medical and psychosocial support in SSc care.

Although none of the participants exhibited serum levels of VEGF or MMP-9 exceeding the established normal reference ranges, significant associations were still observed between these biomarkers and psychological symptoms. This suggests that even within clinically "normal" biomarker levels, individual variation may have physiological or psychological relevance. It highlights the possibility that subclinical elevations or functional sensitivity to these molecules—rather than absolute abnormal levels—may contribute to the emotional and cognitive burden observed in systemic sclerosis. Thus, "normal" levels of angiogenic and inflammatory markers should still be considered in the context of complex, multi-system diseases like SSc. Previous studies have been focused on the different clinical manifestations of scleroderma and VEGF [7, 19-23]. Studies reported that bipolar patients have significantly higher VEGF levels at baseline, and it may be a laboratory method for the diagnosis of major depressive disorder and schizophrenia [8, 24].

Conversely, although MMP-9 had no meaningful correlations with any psychological domains, the positive association between MMP-9 and VEGF suggests that both biomarkers might participate in a shared pathophysiological network. Mediation analyses confirmed that VEGF significantly mediated the relationship between MMP-9 and multiple psychological domains, suggesting that neurovas-

cular and inflammatory mechanisms contribute to emotional distress in systemic sclerosis. This parallel increase in both biomarkers could suggest common pathophysiological events that underlie the fibrotic and vascular hallmarks of scleroderma. A positive feedback regulation between MMP-9 and VEGF has been described [25]. MMP9 is the most prevalent MMP in the central nervous system, and it plays a role in the pathophysiology of schizophrenia and depression [11, 12]. Higher levels of MMP-9 are described in scleroderma [10, 26].

VEGF and MMP-9 are key players in tissue remodeling and disease progression, with potential roles that extend beyond physical symptoms to include neuroimmune and psychological processes. VEGF, known for promoting blood vessel growth, also interacts with neural cells and has been linked to neurodegenerative conditions, suggesting broader functions in the nervous system [27]. MMP-9, involved in neuroinflammation and neurodegeneration, is upregulated by pro-inflammatory mediators and VEGF [28]. Their interaction may influence the extracellular matrix (ECM) and neuroimmune pathways, potentially impacting psychological health [28]. The absence of a clear correlation between MMP-9 and SCL-90-R scores may reflect a more complex or subtle role in systemic sclerosis, one that is not directly expressed through psychological symptoms or masked by other factors in this small sample.

It is worth considering a few possible explanations for these results. First, elevated VEGF could reflect heightened vascular and inflammatory activity, which may increase psychological sensitivity. Second, the relationship between chronic illness and mental health is complex; in scleroderma, factors such as pain, social isolation, and functional decline can intensify psychological distress, especially when compounded by unresolved inflammation. Third, while MMP-9 correlates with VEGF, its lack of association with psychological symptoms suggests it may act mainly through fibrotic and tissue-damage pathways rather than emotional processes. Lastly, reverse causality should be considered; psychological distress itself may elevate VEGF levels, as chronic stress and depression have been shown to increase VEGF *via* neuroendocrine and inflammatory responses [29-31].

4.1. Limitations and Future Directions

These findings support a more holistic approach to SSc treatment, emphasizing the importance of routine screening for psychological distress. Early interventions, such as counseling, psychotherapy, or therapies targeting inflammatory and vascular pathways, may help improve outcomes.

The study's cross-sectional design limits causal interpretation and prevents understanding of how biomarker levels and psychological symptoms interact over time. Additionally, the small sample size may have reduced the ability to detect significant effects, particularly with MMP-9. Future studies should employ longitudinal designs with larger, more diverse cohorts to validate these findings, explore underlying mechanisms, and assess whether therapies targeting VEGF or MMP-9 can provide both psychological and physical benefits.

CONCLUSION

In summary, our data highlight a significant burden of psychological distress in SSc patients and underscore a noteworthy association between VEGF and specific psychological domains. Mediation analyses revealed that VEGF significantly mediated the relationship between MMP-9 and several psychological symptom domains, supporting the hypothesis of an indirect link between extracellular matrix remodeling and psychological distress. These findings highlight the interconnected roles of inflammatory and neurovascular pathways in the emotional and cognitive burden experienced by SSc patients. Given the cross-sectional nature of our study, reverse causality remains plausible, in which psychological distress could elevate VEGF. Chronic inflammation and social stress, which were not directly measured, may also act as confounders. Longitudinal studies are needed to elucidate the directionality and causal pathways.

AUTHORS' CONTRIBUTIONS

The authors confirm their contributions to the paper as follows: M.K., L.S.: Study conception and design; A.N.: Data collection; F.A.: Data curation; F.F., A.R., M.M.E., A.A.: Validation. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

VEGF	=	Vascular Endothelial Growth Factor
MMP-9	=	Matrix Metalloproteinase-9
SSc	=	Systemic Sclerosis
SCL-90-R	=	Symptom Checklist-90-Revised
CNS	=	Central Nervous System
PAH	=	Pulmonary Arterial Hypertension
ILD	=	Interstitial Lung Disease
PAP	=	Pulmonary Arterial Pressure
SOM	=	Somatization
OC	=	Obsessive–compulsive
IS	=	Interpersonal sensitivity
DEP	=	Depression
ANX	=	Anxiety
HOS	=	Hostility
PHOB	=	Phobic anxiety
PI	=	Paranoid Ideation
PSY	=	Psychoticism
GSI	=	Global Severity Index

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This survey was approved by the ethical board of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RETECH.REC.1402.204).

HUMAN AND ANIMAL RIGHTS

AAll human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from all individual participants included in the study.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

FUNDING

None.

CONFLICT OF INTEREST

Leila Simani is the Editorial Advisory Board of the journal TONEUJ.

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