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CLINICAL AND IMMUNOLOGICAL CHARACTERISTICS OF ANGIOGENESIS FACTORS AND ENDOTHELIAL DYSFUNCTION IN DIABETIC FOOT SYNDROME

Rakhmonov Nodir Nuritdinovich
Independent Researcher, Institute of Immunology and Human Genomics, Academy of Sciences of the Republic of Uzbekistan
https://orcid.org/0009-0002-1284-3745
nodir.raxmonov88@mail.ru

Ruzimurodov Nodirjon Fazliddinovich
Deputy Director, Institute of Immunology and Human Genomics, Academy of Sciences of the Republic of Uzbekistan, Doctor of Medical Sciences (DSc)
https://orcid.org/0000-0002-5194-1113
r.ruzimurodov@immuno.uz

Azizova Zukhra Shukhratovna
Senior Researcher, Institute of Immunology and Human Genomics, Doctor of Philosophy in Biological Sciences (PhD)
Academy of Sciences of the Republic of Uzbekistan,
https://orcid.org/0009-0009-8723-3002
zuhra_0203@list.ru

Nazirkulov Olimjan Maxmudjonov
Junior Researcher, Institute of Immunology and Human Genomics, Academy of Sciences of the Republic of Uzbekistan
https://orcid.org/ 0000-0002-0304-3685
nazirkulov88@mail.ru

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Abstract

Objective: To evaluate the clinical and immunological characteristics of angiogenesis factors, tissue repair markers, and endothelial dysfunction in patients with diabetic foot syndrome associated with type 2 diabetes mellitus.

Materials and Methods: The study included patients with type 2 diabetes mellitus with and without diabetic foot syndrome, as well as apparently healthy controls matched by age and sex. Serum concentrations of VEGF-A, IGF-1, TGF-β1, and sVCAM-1 were determined using enzyme-linked immunosorbent assay. Statistical analysis was performed using nonparametric methods.

Results: Patients with diabetic foot syndrome demonstrated a more severe clinical profile characterized by a higher prevalence of obesity, arterial hypertension, cardiovascular disease, diabetic polyneuropathy, retinopathy, nephropathy, and macroangiopathy. Immunological analysis revealed decreased serum levels of VEGF-A and IGF-1 together with elevated TGF-β1 and sVCAM-1 levels. These changes were most pronounced in patients with diabetic foot syndrome and reflected impaired angiogenesis, reduced tissue reparative capacity, endothelial activation, vascular inflammation, and tissue remodeling.

Conclusion: Diabetic foot syndrome in patients with type 2 diabetes mellitus is associated with a combined clinical and immunological profile characterized by suppression of angiogenesis, reduced reparative potential, endothelial dysfunction, and chronic vascular inflammation. Comprehensive assessment of VEGF-A, IGF-1, TGF-β1, and sVCAM-1 may be useful for early identification of patients at high risk for diabetic foot complications.

Keywords: Diabetic foot syndrome; type 2 diabetes mellitus; cytokines; immunity; immune imbalance; angiogenesis; endothelial dysfunction.

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Introduction

Diabetic foot syndrome (DFS) remains one of the most severe complications of type 2 diabetes mellitus (T2DM), as it leads to chronic ulcerative-necrotic lesions, infectious complications, recurrent hospitalizations, and lower-limb amputations [1, 2]. The increasing prevalence of T2DM consequently contributes to a growing number of patients at high risk for vascular and trophic complications. According to the International Diabetes Federation, more than 580 million adults worldwide are currently living with diabetes, while the global NCD-RisC analysis has demonstrated a persistent increase in diabetes prevalence over recent decades [8, 15].

The development of DFS is associated not with a single pathogenic mechanism, but rather with a complex interaction of metabolic, vascular, neurotrophic, and immunoinflammatory disturbances. Chronic hyperglycemia, insulin resistance, oxidative stress, and endothelial dysfunction contribute to micro- and macroangiopathy, impaired microcirculation, tissue hypoxia, and reduced regenerative capacity of tissues [10]. Against this background, diabetic neuropathy and chronic inflammation create favorable conditions for the formation of long-term non-healing ulcers and progression of purulent-necrotic lesions [5, 12].

In recent years, DFS has increasingly been regarded as a clinical manifestation of systemic immunometabolic maladaptation. Within this concept, not only ischemia and infection, but also impaired angiogenesis, endothelial activation, extracellular matrix remodeling, and defective tissue repair are considered critical components of disease progression [7, 14]. Chronic inflammation in diabetes supports dysregulation of macrophage responses, increased expression of proinflammatory mediators and adhesion molecules, thereby preventing the transition of the wound process from the inflammatory phase to полноценной tissue regeneration [3, 5].

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Particular interest has recently been focused on biomarkers reflecting angiogenic-reparative and endothelial-inflammatory regulation. Vascular endothelial growth factor A (VEGF-A) is considered one of the key mediators of neovascularization and vascular permeability, insulin-like growth factor 1 (IGF-1) is involved in cellular proliferation and wound healing, whereas transforming growth factor beta 1 (TGF-β1) regulates inflammation, tissue remodeling, and fibrogenesis [4, 6, 14]. The soluble form of vascular cell adhesion molecule-1 (sVCAM-1) reflects endothelial activation and enhanced vascular inflammation, which is of particular importance in diabetic vascular complications [9, 11].

Despite the considerable number of studies devoted to the pathogenesis of DFS, comprehensive assessment of angiogenesis factors, tissue repair mechanisms, and endothelial dysfunction in patients with T2DM remains insufficiently investigated. Meanwhile, such an approach may improve understanding of the clinical and immunological features underlying the transition from T2DM to DFS and facilitate early identification of patients at high risk for diabetic foot complications.

Objective

The aim of the study was to evaluate the clinical and immunological features of angiogenesis factors, tissue repair mechanisms, and endothelial dysfunction in patients with diabetic foot syndrome associated with type 2 diabetes mellitus.

Materials and Methods

The study was conducted at the clinical base of the Navoi branch of the Republican Specialized Scientific and Practical Medical Center of Endocrinology named after Academician Y.Kh.Turakulov from September 2023 to September 2025.

A total of 84 individuals were enrolled in the study. The main group included 58 patients with type 2 diabetes mellitus (T2DM), among whom 30 patients had

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T2DM without diabetic foot syndrome (DFS), while 28 patients had T2DM complicated by DFS. The control group consisted of 26 apparently healthy individuals matched for age and sex.

The diagnosis of T2DM was established based on clinical and laboratory findings, including medical history, carbohydrate metabolism parameters, and the use of glucose-lowering therapy. Diabetic foot syndrome was diagnosed considering the presence of ulcerative-trophic lesions of the foot, signs of diabetic neuropathy, vascular disorders, and infectious-inflammatory changes in soft tissues.

Clinical examination included medical history assessment, evaluation of T2DM duration, glucose-lowering therapy, concomitant diabetic complications, and vascular-trophic changes in the lower extremities.

Venous blood samples collected in the morning after overnight fasting served as the study material. Following centrifugation, serum samples were used for immunological analyses. Immunological investigations were performed at the Laboratory of Reproductive Immunology of the Institute of Immunology and Human Genomics of the Academy of Sciences of the Republic of Uzbekistan.

Serum concentrations of VEGF-A, IGF-1, TGF-β1, and sVCAM-1 were determined using enzyme-linked immunosorbent assay (ELISA). VEGF-A levels were measured using the VEGF-A-IFA-BEST kit (Vector-Best, Russia); IGF-1 using the IGF-1 ELISA kit (Cloud-Clone Corp.); TGF-β1 using the TGF-β1 ELISA kit (BioChemMac, Russia); and sVCAM-1 using the Human sVCAM-1 ELISA kit (FineTest, China).

Statistical analysis was performed using the Statistica for Windows 6.0 software package. Quantitative variables were presented as median and interquartile range – Me [Q1; Q3]. Distribution normality was assessed using the Shapiro–Wilk test. Intergroup comparisons were performed using the Mann–Whitney U test with Bonferroni correction. Differences were considered statistically significant at $p<0.05$. To evaluate the diagnostic significance of the studied biomarkers, ROC

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analysis was performed with calculation of the area under the curve (AUC), optimal cut-off values, sensitivity, specificity, and Youden index. ROC analysis was aimed at differentiating patients with T2DM from those with progression to diabetic foot syndrome.

Results

Clinical and anamnestic analysis demonstrated that the examined groups were comparable in terms of age and sex, which allowed subsequent comparison of immunometabolic parameters to be performed correctly. The mean age of the entire cohort was 59.1±4.4 years; in the control group it was 58.7±3.9 years, in the T2DM group – 59.2±4.1 years, and in the T2DM+DFS group – 59.4±4.6 years. No statistically significant differences in age were observed between the groups ($p>0.05$). Gender distribution was also comparable: males accounted for 53.8% in the control group, 51.7% among patients with T2DM, and 54.2% in the T2DM+DFS group.

The duration of type 2 diabetes mellitus was similar in patients with T2DM without diabetic foot syndrome and in patients with T2DM+DFS, comprising 4.21±0.63 and 4.37±0.58 years, respectively. However, patients with DFS demonstrated a more unfavorable somatic background. Body mass index in the T2DM+DFS group was higher than in patients with uncomplicated T2DM and reached 31.46±3.12 kg/m² versus 29.83±2.91 kg/m². Overweight and obesity were observed in 81.7% of patients with T2DM+DFS, whereas in the T2DM group these conditions were identified in 68.9% of cases. Arterial hypertension was also more frequent in patients with DFS (79.4% vs. 62.1%), as was cardiovascular pathology (58.6% vs. 41.3%).

Analysis of chronic diabetic complications revealed more pronounced systemic involvement in patients with diabetic foot syndrome. Diabetic polyneuropathy was detected in 87.5% of patients with T2DM+DFS, whereas in the T2DM group without DFS it was identified in 46.6% of patients ($p<0.05$). Diabetic retinopathy

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was registered in 58.3% of DFS patients compared with 31.0% in the T2DM group; diabetic nephropathy in 47.9% versus 24.1%; and diabetic macroangiopathy in 52.1% versus 27.6%, respectively ($p<0.05$). These findings indicate that the development of DFS occurred against a background of more pronounced vascular and neurotrophic impairment.

The clinical structure of DFS was characterized by predominance of the neuroischemic form, identified in 50.0% of patients. The neuropathic form was observed in 27.1% of cases, while the ischemic form accounted for 22.9%. An infectious component was present in the majority of patients: localized soft tissue infection was detected in 43.8%, severe widespread infection in 16.7%, whereas 39.6% of patients had no clinical signs of infection. Deep ulcerative defects predominated over superficial lesions and were observed in 62.5% of patients. The most frequent ulcer localization involved the forefoot, including the metatarsophalangeal region (35.4%), and the toes (29.2%). Recurrent disease course was documented in 58.3% of patients, emphasizing the chronic nature of vascular-trophic impairment in DFS.

Thus, the clinical profile of patients with T2DM+DFS was characterized by a higher prevalence of obesity, arterial hypertension, cardiovascular disease, diabetic polyneuropathy, retinopathy, nephropathy, and macroangiopathy. These findings confirm that diabetic foot syndrome develops not as an isolated local lesion, but against a background of systemic metabolic, vascular, and neurotrophic disturbances. Such a clinical background creates the basis for subsequent assessment of angiogenic-reparative and endothelial-inflammatory biomarkers.

Analysis of immunological parameters showed that T2DM is associated with an imbalance of angiogenic-reparative and endothelial-inflammatory regulation, which becomes more pronounced with the development of diabetic foot syndrome.

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VEGF-A is a key mediator of angiogenesis, vascular permeability, and endothelial cell survival. A decrease in VEGF-A reflects weakening of the angiogenic response and insufficient vascular adaptation of tissues under conditions of hypoxia and chronic inflammation. In the control group, the median VEGF-A level was 115.91 [102.89; 129.64] pg/mL. In patients with T2DM, this parameter decreased to 97.44 [87.27; 122.87] pg/mL ($p<0.001$), while in patients with T2DM+DFS it decreased further to 83.20 [77.37; 103.73] pg/mL ($p<0.001$ compared with controls; $p<0.01$ compared with T2DM).

IGF-1 is involved in the regulation of cellular proliferation, keratinocyte migration, angiogenesis, and wound healing. A decrease in its level may be regarded as a sign of reduced reparative potential. In the control group, the median IGF-1 level was 94.68 [78.25; 101.42] pg/mL. In patients with T2DM, IGF-1 decreased to 77.44 [67.72; 82.36] pg/mL ($p<0.001$), whereas in the T2DM+DFS group it decreased to 66.85 [53.12; 72.42] pg/mL ($p<0.001$ compared with controls; $p<0.01$ compared with T2DM).

Table 1. Serum levels of growth factors in the examined patients

Parameter	Me [Q1; Q3]	p vs. control	p T2DM vs. T2DM+DFS
Control group, n=26			
VEGF-A, pg/ml	115,91 [102,89; 129,64]	–	–
IGF-1, pg/ml	94,68 [78,25; 101,42]		
TGF-β1, pg/ml	40,84 [30,68; 49,99]		
sVCAM-1, ng/ml	238,23 [187,80; 311,13]		
T2DM group, n=30			
VEGF-A, pg/ml	97,44 [87,27; 122,87]	*<0,001**	–
IGF-1, pg/ml	77,44 [67,72; 82,36]	*<0,001**	
TGF-β1, pg/ml	51,74 [44,56; 66,22]	*<0,01**	
sVCAM-1, ng/ml	337,73 [296,37; 364,06]	*<0,001**	
T2DM+DFS group, n=28			
VEGF-A, pg/ml	83,20 [77,37; 103,73]	*<0,001**	*<0,01**
IGF-1, pg/ml	66,85 [53,12; 72,42]	*<0,001**	*<0,01**
TGF-β1, pg/ml	69,13 [58,41; 76,39]	*<0,001**	*<0,01**
sVCAM-1, ng/ml	419,48 [320,53; 584,58]	*<0,001**	*<0,001**

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Note: ** statistically significant differences; Mann–Whitney U test with Bonferroni correction. Me – median; Q1 – 25th percentile; Q3 – 75th percentile.*

TGF-β1 is a multifunctional cytokine involved in the regulation of inflammation, cellular differentiation, tissue remodeling, and fibrogenesis. In contrast to VEGF-A and IGF-1, its level increased in patients with T2DM. In the control group, the median TGF-β1 level was 40.84 [30.68; 49.99] pg/mL. In patients with T2DM, the parameter increased to 51.74 [44.56; 66.22] pg/mL ($p<0.01$), while in patients with T2DM+DFS it further increased to 69.13 [58.41; 76.39] pg/mL ($p<0.001$ compared with controls; $p<0.01$ compared with T2DM). Such elevation indicates activation of fibrogenic and tissue remodeling mechanisms under conditions of chronic inflammation.

sVCAM-1 is a soluble form of vascular cell adhesion molecule and reflects endothelial activation, enhanced leukocyte adhesion, and vascular inflammation. In the control group, the sVCAM-1 level was 238.23 [187.80; 311.13] ng/mL. In patients with T2DM, the median value reached 337.73 [296.37; 364.06] ng/mL, whereas in the T2DM+DFS group it increased to 419.48 [320.53; 584.58] ng/mL. The increase was statistically significant both compared with the control group and between the T2DM and T2DM+DFS groups ($p<0.001$).

Thus, patients with T2DM demonstrated decreased VEGF-A and IGF-1 levels accompanied by simultaneous elevation of TGF-β1 and sVCAM-1. With the development of diabetic foot syndrome, these alterations became more pronounced, reflecting suppression of angiogenesis and tissue repair processes against a background of endothelial activation, vascular inflammation, and tissue remodeling.

Discussion

The obtained data indicate that diabetic foot syndrome in patients with T2DM develops against a background of combined clinical and immunological impairment. Patients with T2DM+DFS had a higher prevalence of obesity,

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arterial hypertension, cardiovascular disease, diabetic polyneuropathy, retinopathy, nephropathy, and macroangiopathy. This clinical profile suggests systemic vascular and metabolic involvement, in which the foot ulcer should not be regarded as an isolated local complication, but rather as a clinical manifestation of long-standing metabolic, neurotrophic, and endothelial dysfunction.

Immunological alterations should be interpreted in the context of these clinical characteristics. The predominance of the neuroischemic form of DFS, together with the high frequency of deep ulcerative defects and recurrent disease course, indicates marked impairment of microcirculation, tissue hypoxia, and insufficient reparative response. Against this background, decreased VEGF-A levels in patients with T2DM+DFS reflect weakened angiogenic compensation under conditions of chronic ischemia. In other words, the affected tissues require restoration of the vascular network, whereas the systemic angiogenic response appears to be insufficient.

The decrease in IGF-1 further supports this pattern and indicates reduced reparative potential of tissues. In the presence of deep and recurrent ulcerative defects, this finding is of particular importance, since IGF-1 is involved in cellular proliferation, keratinocyte migration, granulation tissue formation, and wound healing. Therefore, reduced IGF-1 levels in patients with DFS may be associated with delayed epithelialization, instability of the wound process, and a tendency of ulcers to recur.

The increase in TGF-β1 in patients with T2DM, and especially in those with T2DM+DFS, reflects another, not always effective, type of tissue response. On the one hand, TGF-β1 participates in the regulation of inflammation and tissue remodeling; on the other hand, under conditions of chronic inflammation, its elevation may be accompanied by fibrogenic remodeling, disruption of extracellular matrix architecture, and incomplete repair. Clinically, this is consistent with the predominance of deep ulcerative defects and the chronic

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course of DFS, when inflammation persists but complete tissue restoration does not occur.

The most pronounced increase in sVCAM-1 in patients with T2DM+DFS confirms the involvement of endothelial activation and vascular inflammation in the progression of diabetic foot lesions. The high prevalence of macroangiopathy, cardiovascular disease, and the neuroischemic form of DFS clinically supports this observation. Increased sVCAM-1 reflects enhanced leukocyte adhesion to the endothelium, inflammatory injury of the vascular wall, and impaired microcirculation, thereby creating conditions for ischemia, chronicity of the ulcerative process, and delayed wound healing.

Thus, patients with T2DM+DFS demonstrate a characteristic clinical and immunological profile: on the one hand, pronounced vascular-neuropathic involvement, deep ulcerative defects, and recurrent disease course; on the other hand, decreased VEGF-A and IGF-1 levels accompanied by elevated TGF-β1 and sVCAM-1. This combination reflects a gap between the tissue demand for angiogenesis and repair and the actual inability of the organism to provide an adequate restorative response. This imbalance may underlie the transition of T2DM from a metabolic disorder to a severe vascular-trophic complication manifested as diabetic foot syndrome.

The obtained results suggest that VEGF-A, IGF-1, TGF-β1, and sVCAM-1 may be considered informative clinical and immunological biomarkers reflecting different aspects of the pathogenesis of diabetic foot syndrome, including impaired angiogenesis, reduced reparative potential, tissue remodeling, and endothelial inflammation. Their combined assessment may be useful for earlier identification of patients at high risk of unfavorable T2DM progression and development of diabetic foot lesions.

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Conclusions

1. Patients with T2DM+DFS demonstrated a clinical profile characterized by a higher prevalence of obesity, arterial hypertension, cardiovascular disease, diabetic polyneuropathy, retinopathy, nephropathy, and macroangiopathy, confirming the systemic nature of vascular and metabolic involvement.
2. Patients with T2DM exhibited decreased serum levels of VEGF-A and IGF-1, with the most pronounced reduction observed in patients with diabetic foot syndrome, indicating suppression of angiogenesis and tissue repair processes.
3. TGF-β1 levels increased in patients with T2DM and reached maximal values in patients with T2DM+DFS, reflecting activation of tissue remodeling and fibrogenic processes under conditions of chronic inflammation.
4. Elevated sVCAM-1 levels in patients with T2DM+DFS indicate enhanced endothelial activation, vascular inflammation, and leukocyte adhesion contributing to chronicity of the ulcerative-trophic process.
5. Comprehensive assessment of VEGF-A, IGF-1, TGF-β1, and sVCAM-1 may be applied as a clinical and immunological approach for characterization of the risk of development and progression of diabetic foot syndrome in patients with T2DM.

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