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Endothelial And Extracellular Matrix Biomarkers In Diabetic Foot Disease Among Patients With Type 2 Diabetes Mellitus

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Abstract: Type 2 diabetes mellitus (T2DM) remains a major cause of chronic vascular disease and disability, and delayed diagnosis often means the condition is first recognized after complications have developed. Diabetic foot syndrome (DFS) is one of the most severe T2DM complications, arising from ischemia, neuropathy, and chronic inflammation and leading to ulceration, prolonged treatment, and a high risk of amputation. To determine the pattern and magnitude of changes in serum sVCAM-1 and MMP-9 levels in patients with T2DM depending on the presence of DFS. The study enrolled 58 men and women aged 50–65 years with T2DM, divided into an uncomplicated T2DM group (n=30) and a T2DM+DFS group (n=28); 26 age- and sex-matched apparently healthy individuals served as controls. Serum sVCAM-1 and MMP-9 were measured by ELISA using certified kits, and between-group differences were assessed with $p<0.05$ considered statistically significant. Serum sVCAM-1 was significantly elevated in patients with type 2 diabetes mellitus compared with controls and increased further in those with diabetic foot syndrome ($p < 0,001$). Serum MMP-9 showed the same pattern, being significantly higher in uncomplicated type 2 diabetes than in controls and reaching the highest levels in the diabetic foot group ($p < 0,001$). Overall, both biomarkers demonstrated a stepwise, statistically significant rise from controls to uncomplicated diabetes and to diabetes complicated by diabetic foot syndrome, consistent with more pronounced endothelial activation and inflammation-associated proteolytic remodeling in DFS.

Keywords: Type 2 diabetes mellitus, biomarkers, diabetic foot disease, VCAM-1, Mmp-9.

Introduction: Type 2 diabetes mellitus (T2DM) remains a major driver of chronic vascular disease and disability. According to the International Diabetes Federation (IDF), diabetes affects hundreds of millions of adults, and a substantial proportion of cases are still undiagnosed, increasing the likelihood that the disease is first detected at the stage of complications [8].

Diabetic foot syndrome (DFS) is among the most severe complications of T2DM. It arises from the interplay of ischemia, neuropathy, and chronic inflammation, leading to ulcer formation, prolonged treatment courses, and a heightened risk of lower-limb amputation. Even after ulcer closure, the risk of recurrence remains high; therefore, this state is often regarded as remission rather than complete recovery [1, 13]. International guidance emphasizes early risk stratification and routine patient screening (IWGDF, 2023) [9]. However, clinical practice still lacks readily available laboratory markers that capture the key pathogenic mechanisms of DFS.

Endothelial dysfunction is a central element in the

vascular complications of T2DM, sustaining a prothrombotic and pro-inflammatory phenotype within the microvasculature [7]. In this context, assessing endothelial (sVCAM-1) and extracellular matrix–related (MMP-9) biomarkers in T2DM and DFS is a promising approach for refining pathogenetic understanding, improving risk stratification, and enabling personalized monitoring.

Study objective – to characterize the pattern and magnitude of changes in serum sVCAM-1 and MMP-9 levels in patients with type 2 diabetes mellitus, according to the presence or absence of diabetic foot syndrome.

METHODS

The study included 58 men and women aged 50–65 years with an established diagnosis of T2DM. Participants were allocated to two groups: the T2DM group (n = 30), comprising patients with type 2 diabetes mellitus without complications, and the T2DM+DFS group (n = 28), comprising patients with diabetic foot syndrome that developed in the setting of T2DM. The control group consisted of 26 apparently healthy individuals matched for age and sex.

Eligible participants were men and women aged 50–65 years with a clinically and laboratory confirmed diagnosis of T2DM established no more than 5 years prior to enrollment, and with compensated or subcompensated carbohydrate metabolism. Written informed consent was obtained from all participants.

Exclusion criteria were type 1 diabetes mellitus; acute inflammatory or infectious conditions; chronic renal or hepatic failure; malignancy; autoimmune diseases and systemic vasculitides. Individuals who had received immunomodulators, glucocorticosteroids, or cytotoxic agents within 3 months prior to inclusion were also excluded.

All patients underwent comprehensive clinical, laboratory, and instrumental evaluation. Anthropometric measures (body weight, height, body mass index) and blood pressure were recorded. Carbohydrate metabolism indices (fasting plasma glucose, glycated hemoglobin – HbA1c), lipid profile parameters, and insulin resistance index (HOMA-IR) were assessed. Lower-limb vascular status was evaluated using ultrasonography, Doppler sonography, and angiography when clinically indicated.

Immunological assays were performed at the Laboratory of Reproductive Immunology, Institute of Immunology and Human Genomics, Academy of Sciences of the Republic of Uzbekistan. Biological samples were collected at the clinical base of the Navoi Branch of the Republican Specialized Scientific and Practical Medical Center of Endocrinology named after Academician Yo.Kh. Turakulov. Serum levels of soluble vascular cell adhesion molecule-1 (sVCAM-1; Human sVCAM-1 ELISA) and matrix metalloproteinase-9 (MMP-9; Human MMP-9 ELISA) were measured by enzyme-linked immunosorbent assay (ELISA) using certified kits (FineTest, China; CUSABIO, China) in accordance with the manufacturers' instructions.

Statistical analysis was performed using Statistica for Windows 6.0 (StatSoft Inc., USA). Quantitative variables are presented as the mean ± standard error of the mean (M ± m), as well as the median with interquartile range, Me [Q1; Q3]. Comparisons between independent groups were conducted using the two-tailed Student's t test for independent samples. The 95% confidence intervals (95% CI) for the mean were calculated based on the t distribution. Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Chronic hyperglycaemia in T2DM initiates early endothelial activation, which is regarded as a pivotal mechanism of vascular remodelling and the progression of ischaemic complications, including diabetic foot syndrome (DFS) [3].

VCAM-1 (CD106) belongs to the immunoglobulin superfamily of adhesion molecules and is a cytokine-inducible glycoprotein expressed predominantly by activated endothelial cells. Its interaction with the leukocyte integrin α4β1 (VLA-4) mediates firm adhesion and transendothelial migration – an essential step in chronic inflammation of the vascular wall and in atherogenesis [15]. Review data indicate that the soluble form, sVCAM-1, is generated mainly through proteolytic shedding of membrane-bound VCAM-1 by metalloproteinases; therefore, it can be considered a circulating marker of endothelial activation and injury [16].

Table 1.

Serum levels of soluble adhesion molecules in the examined patients

Parameter	*M±m*, ng/mL	Me [Q1; Q3]	95% CI	*p-value*
Control group, n=26				

sVCAM-1	250,28±18,56	238,23 [187,80; 311,13]	212,05-288,53	-
T2DM group, n=30				
sVCAM-1	340,62±8,95	337,73 [296,37; 364,06]	322,32–358,97	*<0,001**
T2DM + DFS group, n=28				
sVCAM-1	439,70±23,96	419,48 [320,53; 584,58]	390,53–488,87	*<0,001*#*

Note: * — statistically significant vs the control group; # — statistically significant vs the T2DM group. Me, median; Q1 (percentile), 25%; Q3 (percentile), 75%.

Analysis of the results showed that serum sVCAM-1 was significantly higher in patients with T2DM than in the control group. The mean level in the T2DM group was 340.62 ± 8.95 ng/mL versus 250.28 ± 18.56 ng/mL in controls, i.e., approximately 1.4-fold higher. The median value in this group was 337.73 ng/mL [296.37–364.60], with a 95% CI of 322.32–358.97, and the difference was statistically significant ($p < 0.001$) (Table 1).

In patients with DFS in the context of T2DM, sVCAM-1 increased even more markedly. The mean level was 439.70 ± 23.96 ng/mL, which was 1.7-fold higher than the control values and 1.3-fold higher than in patients with uncomplicated T2DM. The median reached 419.48 ng/mL [320.53–584.58], with a 95% CI of 390.53–488.87, and this difference was also statistically significant ($p < 0.001$). On direct comparison between the T2DM and T2DM+DFS groups, sVCAM-1 levels in patients with DFS were approximately 1.3-fold higher, and the between-group difference remained statistically significant ($p < 0.001$) (Table 1).

Matrix metalloproteinase-9 (MMP-9; gelatinase B; also described as a 92-kDa type IV collagenase) belongs to the matrix metalloproteinase family–zinc–containing, calcium-dependent endopeptidases that mediate controlled proteolysis of extracellular matrix (ECM) components [11, 2].

Functionally, MMP-9 contributes to the degradation of structural ECM proteins and basement membranes (including gelatin/denatured collagen and collagens) and can also proteolytically modify a range of extracellular signalling molecules, thereby shaping the inflammatory response and reparative processes [10, 4].

MMP-9 is produced by both inflammatory cells (macrophages and neutrophils) and resident tissue

Table 2.

Serum levels of extracellular matrix remodelling factors in the examined patients

Parameter	*M±m*, ng/mL	Me [Q1; Q3]	95% CI	*p-value*
Control group, n=26				
MMP-9	98,64±2,53	97,68 [92,35; 108,81]	93,43–103,86	-
T2DM group, n=30				
MMP-9	159,01±7,10	149,32 [121,57; 196,54]	144,49–173,54	*<0,001**
T2DM + DFS group, n=28				
MMP-9	335,62±13,84	316,29 [291,70; 411,38]	307,23–364,02	*<0,001*#*

Note: * — statistically significant vs the control group; # — statistically significant vs the T2DM group. Me, median; Q1 (percentile), 25%; Q3 (percentile), 75%.

The analysis demonstrated that MMP-9 levels in patients with T2DM were significantly higher than in the control group. Specifically, the mean value in the T2DM group was 159.01 ± 7.10 ng/mL, which is 1.6-fold higher than the control level (98.64 ± 2.53 ng/mL). In

T2DM, the median reached 149.32 ng/mL [121.57–196.54], with a 95% CI of 144.49–173.53, indicating a statistically significant increase ($p < 0.001$).

In the group of patients with T2DM complicated by DFS, MMP-9 rose even more substantially. The mean level was 335.62 ± 13.84 ng/mL, exceeding the control values by 3.4-fold and the values in uncomplicated T2DM by 2.1-fold. The median in DFS was 316.29 ng/mL [291.70–411.38], with a 95% CI of 307.23–364.02, and the increase was statistically significant ($p < 0.001$). When comparing the T2DM and T2DM+DFS groups directly, MMP-9 in DFS was approximately 2.1-fold higher, and the between-group difference remained statistically significant ($p < 0.001$) (Table 2).

Thus, our study identified a significant rise in serum sVCAM-1 and MMP-9, with higher levels in patients with T2DM and the highest levels in T2DM complicated by DFS; between-group differences remained statistically significant. The observed changes likely reflect intensifying systemic endothelial activation and an inflammation-driven proteolytic imbalance as vascular and tissue injury becomes more severe in T2DM.

Elevated sVCAM-1 in T2DM is likely attributable to the fact that chronic hyperglycaemia, insulin resistance, and oxidative stress sustain pro-inflammatory endothelial activation and upregulate adhesion molecule expression, thereby facilitating leukocyte recruitment and perpetuating chronic vascular inflammation. Our findings are consistent with the study by Theocharidis et al. (2020), which suggests that the additional increase in sVCAM-1 observed in DFS may result from the combined effects of ischaemia, local infection/contamination, tissue hypoxia, and systemic low-grade inflammation. Prospective studies using multiplex panels indicate that such a low-intensity inflammatory milieu is characteristic of patients with non-healing diabetic ulcers [14].

The increase in MMP-9 in T2DM, and its more pronounced rise in T2DM+DFS, likely reflects heightened proteolytic activity and dysregulated extracellular matrix remodelling, which may impede the transition of the wound from the inflammatory phase to the reparative phase. These observations are supported by systematic reviews and contemporary mechanistic studies emphasizing that excessive MMP-9 promotes persistent inflammation, extracellular matrix degradation, and impaired angiogenesis in DFS [12, 6].

CONCLUSION

The present results indicate that T2DM – particularly when complicated by DFS – is associated with a more prominent systemic phenotype of endothelial dysfunction (sVCAM-1) and inflammation-driven proteolytic remodelling (MMP-9). These findings support further evaluation of the prognostic utility of these biomarkers, especially in relation to the severity of ischaemia/infection and wound-healing outcomes, in larger and clinically stratified cohorts.

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