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Immunometabolic Predictors Of Diabetic Foot Syndrome In Type 2 Diabetes Mellitus

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Abstract: Background. Diabetic foot syndrome (DFS) is one of the most severe complications of type 2 diabetes mellitus (T2DM), developing through a complex interaction of chronic hyperglycemia, insulin resistance, endothelial activation, adipokine imbalance, impaired tissue remodeling and persistent inflammation. Identification of clinically meaningful biomarkers may improve early risk assessment and prevention of severe trophic complications.

Objective. To evaluate the contribution of clinical, metabolic and immunometabolic factors to the development of DFS in patients with T2DM and to develop a predictive model for risk stratification.

Materials and methods. The study included patients with T2DM with and without DFS, as well as a control group of conditionally healthy individuals. Clinical and laboratory parameters, indices of carbohydrate and lipid metabolism, insulin resistance, adipokine status, endothelial activation and extracellular matrix remodeling were analyzed. Logistic regression analysis was used to identify predictors associated with DFS. ROC analysis was performed to assess the diagnostic value of selected biomarkers. The most informative predictors were integrated into the BGU database-based immunometabolic risk model.

Results. Univariate regression analysis showed that body mass index, arterial hypertension, HbA1c, fasting glucose, HOMA-IR, lipid profile parameters, leptin, adiponectin, VEGF-A, IGF-1, TGF-β1, sVCAM-1 and MMP-9 were associated with DFS risk. In multivariate analysis, five independent predictors retained statistical significance: HbA1c, HOMA-IR, adiponectin, sVCAM-1 and MMP-9. ROC analysis demonstrated the highest diagnostic performance for MMP-9, with an AUC of 0.993, cut-off value of 258.9 ng/mL, sensitivity of 92.9% and specificity of 100.0%. Adiponectin and sVCAM-1 also showed clinically relevant diagnostic value. Based on these findings, an integrated model was developed to classify patients into low, moderate and high DFS risk categories.

Conclusion. DFS in T2DM is associated not with a single isolated factor, but with a combined pattern of chronic hyperglycemia, insulin resistance, reduced protective adipokine activity, endothelial activation and matrix destruction. The proposed immunometabolic model may support early identification of high-risk patients and improve personalized prevention of diabetic foot complications.

Keywords: Diabetic foot syndrome, type 2 diabetes mellitus, insulin resistance, systemic inflammation, adiponectin, sVCAM-1, MMP-9, ROC analysis, risk stratification.

Introduction: Diabetic foot syndrome remains one of the most clinically significant complications of type 2 diabetes mellitus. Traditionally, DFS has been considered mainly as a local manifestation of diabetic neuropathy, ischemia, ulceration and infection. However, current understanding increasingly supports the view that DFS is a systemic complication resulting from the interaction of metabolic, vascular, inflammatory and tissue-reparative disorders.

The development of DFS cannot be explained only by the duration of diabetes or the presence of hyperglycemia. Patients with comparable disease duration may have different clinical outcomes: some remain relatively stable for years, whereas others develop progressive vascular-trophic lesions of the lower extremities. This indicates that additional pathogenetic mechanisms, including insulin resistance, adipokine imbalance, endothelial activation and matrix remodeling, may determine the risk and severity of diabetic foot complications.

Insulin resistance plays an important role in the progression of T2DM and its vascular complications. It is closely associated with chronic hyperglycemia, atherogenic dyslipidemia, low-grade systemic inflammation and endothelial dysfunction. In the context of diabetic foot syndrome, these changes may impair microcirculation, delay tissue repair and promote chronic wound formation.

In recent years, increasing attention has been given to immunometabolic biomarkers that reflect different levels of DFS pathogenesis. HbA1c and HOMA-IR characterize chronic hyperglycemia and insulin resistance; adiponectin reflects protective adipokine activity; sVCAM-1 indicates endothelial activation and leukocyte adhesion; MMP-9 reflects extracellular matrix degradation and inflammatory tissue remodeling. The combined evaluation of these markers may provide more clinically useful information than isolated assessment of single laboratory indicators.

Therefore, the aim of the present study was to analyze the role of clinical, metabolic and immunometabolic factors in the development of DFS in patients with T2DM and to develop a practical risk stratification model based on the most informative predictors.

Materials and Methods

The study was designed as an open, prospective, comparative clinical and laboratory study with parallel groups. The total sample included 132 participants divided into three groups: conditionally healthy controls, patients with T2DM without diabetic foot syndrome, and patients with T2DM complicated by DFS.

The clinical assessment included analysis of anthropometric data, body mass index, presence of arterial hypertension, duration and clinical course of T2DM, and signs of vascular-trophic complications of the lower extremities. Laboratory evaluation included parameters of carbohydrate metabolism, lipid metabolism, insulin resistance and selected immunometabolic markers.

The following parameters were included in the regression analysis: body mass index, arterial hypertension, HbA1c, fasting glucose, HOMA-IR, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, leptin, adiponectin, VEGF-A, IGF-1, TGF-β1, sVCAM-1 and MMP-9.

Univariate logistic regression analysis was first performed to identify factors associated with DFS risk. Variables with clinical and pathogenetic relevance were then included in multivariate regression analysis to determine independent predictors. ROC analysis was used to evaluate the diagnostic performance of selected biomarkers and to determine their optimal cut-off values, sensitivity, specificity and Youden index.

Based on the results of multivariate regression and ROC analysis, an immunometabolic risk stratification model was developed using the BGU patient database: “Tizimli yallig‘lanish sharoitida diabetik oyoq sindromida immunometabolik biomarkerlar paneli”. The database was registered in the State Register of Databases of the Republic of Uzbekistan under No. BGU2290 dated 28 October 2025.

Results

Univariate regression analysis demonstrated that DFS risk was associated with several interrelated groups of factors. Among general clinical parameters, body mass index was significantly associated with DFS risk, with an odds ratio of 1.18. Arterial hypertension also increased the probability of DFS, with an odds ratio of 2.36.

Metabolic parameters showed strong associations with DFS. HbA1c was significantly associated with increased risk, with an odds ratio of 1.86, indicating the importance of chronic hyperglycemia. Fasting glucose also demonstrated a significant association, with an odds ratio of 1.41. HOMA-IR showed one of the

strongest metabolic associations, with an odds ratio of 2.14, confirming the pathogenetic relevance of insulin resistance in the development of DFS.

Lipid metabolism also contributed to DFS risk. Total cholesterol, LDL cholesterol and triglycerides were positively associated with DFS, whereas HDL cholesterol showed a protective direction of association. These findings indicate that atherogenic dyslipidemia contributes to vascular-trophic damage in patients with T2DM.

Table 1.

Independent predictors of diabetic foot syndrome in multivariate regression analysis

Predictor	β-coefficient	OR (95% CI)	p-value
HbA1c	0.49	1.63 (1.11–2.39)	0.013
HOMA-IR	0.61	1.84 (1.24–2.72)	0.002
Adiponectin	-0.32	0.73 (0.58–0.92)	0.008
sVCAM-1	0.54	1.71 (1.17–2.49)	0.005
MMP-9	0.58	1.79 (1.21–2.65)	0.003

Among adipokine markers, leptin was positively associated with DFS risk, whereas adiponectin showed an inverse association. This suggests that adipokine imbalance may participate in the transition from relatively stable T2DM to a complicated vascular-trophic phenotype.

Among endothelial and matrix remodeling markers, sVCAM-1 and MMP-9 demonstrated particularly strong associations. sVCAM-1 reflected endothelial activation and leukocyte adhesion, whereas MMP-9 reflected extracellular matrix degradation and chronic tissue destruction. These markers were among the most important immunometabolic indicators linked to DFS.

In multivariate regression analysis, five predictors retained independent significance: HbA1c, HOMA-IR, adiponectin, sVCAM-1 and MMP-9. HbA1c remained independently associated with DFS risk, with an odds ratio of 1.63. HOMA-IR also retained significance, with an odds ratio of 1.84. Adiponectin showed a protective association, with an odds ratio of 0.73. sVCAM-1 and MMP-9 remained independent predictors, with odds ratios of 1.71 and 1.79, respectively.

These findings suggest that the core predictors of DFS are not random laboratory abnormalities, but represent key pathogenetic mechanisms: chronic hyperglycemia, insulin resistance, reduced protective adipokine reserve, endothelial activation and extracellular matrix destruction.

Table 2.

Diagnostic performance of selected immunometabolic biomarkers

Marker	AUC	Cut-off	Sensitivity	Specificity
MMP-9	0.993	258.9 ng/mL	92.9%	100.0%
Adiponectin	0.812	12.9 µg/mL	78.6%	73.3%
sVCAM-1	0.702	–	46.4%	100.0%
IGF-1	0.674	–	–	–
VEGF-A	0.609	–	–	–
TGF-β1	0.228	Not informative	–	–

ROC analysis demonstrated that MMP-9 had the highest diagnostic performance among the analyzed immunometabolic biomarkers. The AUC for MMP-9 was 0.993, with an optimal cut-off value of 258.9 ng/mL, sensitivity of 92.9%, specificity of 100.0% and Youden index of 0.929. These values indicate that MMP-9 may serve as one of the strongest laboratory indicators of DFS among the studied markers.

Adiponectin also showed good diagnostic value, with an AUC of 0.812, cut-off value of 12.9 µg/mL, sensitivity

of 78.6%, specificity of 73.3% and Youden index of 0.519. This confirms that a decrease in adiponectin reflects the loss of protective metabolic regulation in patients with DFS.

sVCAM-1 showed moderate diagnostic performance, with an AUC of 0.702. Although sensitivity was relatively low at 46.4%, specificity reached 100.0%. This means that sVCAM-1 is less suitable for screening purposes, but may be useful for confirming pronounced endothelial involvement in patients with suspected or established DFS.

Table 3.

BGU-based risk stratification categories

Risk category	Integrated risk index	Clinical interpretation
Low risk	<0.30	Relatively stable T2DM course and low probability of DFS
Moderate risk	0.30–0.59	Presence of metabolic and immunoinflammatory prerequisites requiring dynamic monitoring
High risk	≥0.60	High probability of DFS development or progression requiring intensive monitoring and therapy correction

IGF-1 and VEGF-A demonstrated lower diagnostic performance, with AUC values of 0.674 and 0.609, respectively. Although both markers are pathogenetically related to impaired angiogenesis and tissue repair, their independent diagnostic value was limited. TGF-β1 did not demonstrate acceptable diagnostic value, with an AUC of 0.228.

Based on regression and ROC results, five indicators were included in the final immunometabolic model: HbA1c, HOMA-IR, adiponectin, sVCAM-1 and MMP-9. These variables represented five pathogenetic blocks: chronic hyperglycemia, insulin resistance, adipokine imbalance, endothelial activation and matrix destruction.

The BGU-based model calculated an integrated risk index and stratified patients into three categories: low risk, moderate risk and high risk. An index below 0.30 indicated low risk; values from 0.30 to 0.59 indicated moderate risk; and values of 0.60 or higher indicated high risk of DFS development or progression.

Discussion

The results of this study show that DFS is not determined by a single clinical or laboratory abnormality. Rather, it develops through a combination of metabolic, vascular, inflammatory and tissue-destructive mechanisms. This is supported by the fact that several biomarkers showed significant associations in univariate analysis, while only a limited number retained independent predictive value in multivariate analysis.

The independent role of HbA1c confirms that chronic hyperglycemia remains a central factor in diabetic complications. However, HbA1c alone cannot fully explain DFS development. HOMA-IR also remained an independent predictor, indicating that insulin resistance has its own pathogenetic significance. This finding is important because it suggests that patients with similar diabetes duration may differ in DFS risk depending on the depth of metabolic dysregulation.

The inverse association of adiponectin with DFS risk indicates the loss of protective adipokine activity in patients with vascular-trophic complications. Adiponectin is known to be linked with anti-inflammatory and insulin-sensitizing effects; therefore, its reduction may contribute to chronic low-grade inflammation, endothelial dysfunction and worsening tissue repair.

sVCAM-1 was identified as an independent marker of endothelial activation. Its high specificity suggests that elevated sVCAM-1 may indicate a pronounced vascular-inflammatory component in DFS. Although its sensitivity was moderate, its inclusion in the integrated model is justified by its pathogenetic relevance and independent association with disease risk.

MMP-9 was the most informative marker in the study. Its very high AUC and independent significance in regression analysis indicate that extracellular matrix degradation and tissue remodeling are central mechanisms in DFS progression. The role of MMP-9 is especially important because diabetic foot ulcers are characterized by chronic non-healing tissue injury, impaired repair and persistent inflammatory destruction.

The final model did not include all studied biomarkers. VEGF-A, IGF-1 and TGF-β1 are biologically relevant, but

their diagnostic performance was not sufficient for inclusion in the practical predictive model. This is an important methodological point: the model was constructed not by maximizing the number of variables, but by selecting markers with independent, clinically interpretable and diagnostically meaningful value.

The BGU-based model provides an opportunity to move from isolated biomarker interpretation to integrated risk assessment. In clinical practice, this may support earlier identification of patients with unfavorable immunometabolic profiles and allow timely intensification of monitoring, metabolic correction and preventive care before the development of severe trophic lesions.

Conclusion

The development and clinical progression of diabetic foot syndrome in patients with type 2 diabetes mellitus are associated with a complex immunometabolic pattern that includes chronic hyperglycemia, insulin resistance, reduced adiponectin activity, endothelial activation and extracellular matrix remodeling.

HbA1c, HOMA-IR, adiponectin, sVCAM-1 and MMP-9 were identified as independent predictors of DFS risk. Among the studied biomarkers, MMP-9 demonstrated the highest diagnostic performance, while adiponectin and sVCAM-1 provided additional metabolic and endothelial information.

The proposed BGU-based immunometabolic model allows integrated assessment of DFS risk and stratification of patients into low, moderate and high-risk categories. This approach may improve early prediction of diabetic foot complications, support personalized monitoring and contribute to prevention of severe vascular-trophic outcomes in patients with T2DM.

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