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Integrative Predictive and Prognostic Value of Biomarkers in Diabetic Foot Complications

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ABSTRACT

***Background**: Diabetic foot ulcers (DFU) are devastating complications with high rates of morbidity, amputation, and mortality. Traditional inflammatory markers are not specific in discriminating localized inflammation from the severity of systemic inflammation, and biomarkers are required for adequate risk stratification. **Objective**: This study aimed to assess the combined predictive and prognostic value of presepsin, mid-regional pro-adrenomedullin (MR-proADM), and endocan in evaluating DFU severity and predicting poor clinical outcomes. **Materials and Methods**: A total of 120 patients with DFU were enrolled in a prospective observational study and stratified according to the Wagner grade (0-5). Serum presepsin, MR-proADM, endocan, and conventional inflammatory parameters were determined at the time of admission. Clinical outcomes (healing, chronic wounds, amputation, and mortality) were followed. **Results**: Novel biomarkers were significantly and progressively elevated with increasing severity of the Wagner grade ($p < 0.001$). Patients with adverse events (major amputation, death) had remarkably elevated levels of presepsin, MR-proADM, and endocan compared with those with completely healed wounds. All three biomarkers were strongly associated with the Wagner grade and classical markers ($p < 0.001$). ROC analysis showed excellent discriminatory ability (AUC > 0.91), resulting in a combined biomarker score with a predictive value of AUC = 0.923. Univariate logistic regression showed that MR-proADM (OR = 7. 331), endocan (OR = 2. **Conclusions**: Presepsin, MR-proADM, and endocan are powerful and independent predictive markers of DFU. Their continuous increase parallels tissue damage and systemic decompensation, and they have better predictive power for adverse outcomes than traditional markers.*

Keywords: Diabetic Foot; Biomarkers; Prognosis; Amputation; Sepsis.

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INTRODUCTION

Diabetic foot ulcers (DFUs) are among the most incapacitating and costly complications of diabetes, significantly impacting patients and healthcare systems worldwide. DFUs occur in approximately 18.6 million people worldwide every year and are the cause of up to 80% of lower extremity amputations in patients with diabetes, accompanied by significantly elevated rates of morbidity and mortality [1]. The pathophysiology of DFU is not a simple matter of a single disease but rather a complex combination of peripheral neuropathy, peripheral arterial occlusive disease (PAOD), biomechanical alterations, and changed immune reactions [2]. When infected, these ulcers may rapidly advance to extensive soft tissue necrosis, osteomyelitis, and sepsis, resulting in major amputation in 10–20% of cases [1] [3]. The five-year mortality rate for a person with a diabetic foot

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ulcer (DFU) is ~30% and >70% for those who undergo major amputation [1]. Therefore, early identification of patients at high risk for poor prognosis is essential to provide timely and appropriate interventions to decrease the rates of amputation and death.

Conventional inflammatory markers, namely WBC count, ESR, and CRP, are commonly employed to evaluate the severity of diabetic foot infections. However, these biomarkers frequently do not have the specificity required to distinguish localized inflammation from a profound systemic infectious process, and they may be elevated in other non-infectious conditions [4][5].

Recently, a few promising biomarkers have been identified in the fields of sepsis and ED. Presepsin, a soluble CD14 receptor fragment, is liberated into circulation after monocyte activation by bacterial lipopolysaccharides, which is the leading cause of bacterial infection and sepsis [5]. Therefore, it should also be considered a potential specific marker of bacterial infection and sepsis [6]. Mid-regional pro-adrenomedullin (MR-proADM) is a stable fragment of adrenomedullin, which plays a role in microcirculation and endothelial permeability. Elevated levels of MR-proADM were strongly related with organ failure and death in septic patients [7] [8]. Endocan (endothelial cell-specific molecule-1), a soluble proteoglycan secreted by vascular endothelial cells, has been reported as a marker of endothelial dysfunction and angiogenesis, and its expression is upregulated by pro-inflammatory cytokines in diabetic microvascular complications [9] [10].

Although the prognostic role of each of these biomarkers is well established in systemic infections and critically ill patients, their usefulness when applied in a combined manner for the prediction of negative clinical outcomes in patients with DFU complications has not been sufficiently investigated. Thus, the purpose of this study was to assess the combined predictive and prognostic value of presepsin, MR-proADM, and endocan in patients with DFU complications and to analyze whether they could predict the severity of the disease and the likelihood of negative outcomes, such as major amputation and death.

METHODOLOGY

Study Design and Patient Population

This was a prospective observational study of 120 patients with DFU who were hospitalized at our hospital The blood samples were collected during the period 8/1/2026 to 15/4/2026. All patients in the study were referred and diagnosed in the Diabetic and Endocrine Center in Marjan Medical City, The practical side of the study was performed at the laboratory of chemistry and Biochemistry Department/ College of Medicine. The diagnosis of DFU was made on clinical grounds, and the Wagner grading system was used to classify the severity of the ulcers [11]. Patients were divided into four groups according to their Wagner grade: Group 1 (Wagner grade 0, n=30), group 2 (wagner grades 1-2, n=30), group 3 (wagner grades 3-4, n=30), and group 4 (wagner grades 4-5, n=30). Patients with major comorbidities, such as end-stage renal disease (ESRD), hepatic failure, active malignancies, or associated severe sepsis not related to diabetic foot disease, were excluded.

Clinical Assessment and Outcomes

A comprehensive clinical history was obtained from all participants, including age, BMI, and duration of diabetes mellitus. The primary clinical outcomes assessed during the follow-up period included complete wound healing, development of a chronic nonhealing wound, requirement for minor amputation, requirement for major amputation, and all-cause mortality.

Laboratory Measurements and Biomarker Analysis

The blood samples were collected from all patients upon admission after a standard 12-hour overnight fast. Routine biochemical parameters, including (FBG, HbA1c, WBC count, ESR, CRP, PCT, and serum creatinine levels, were measured using standard automated laboratory techniques.

For quantification of the novel biomarkers, serum samples were centrifuged, aliquoted, and stored at −80°C until analysis. Serum presepsin levels were determined using highly sensitive CLEIA [5]. Plasma MR-proADM concentrations were measured using a TRACE assay [7]. Serum endocan levels were quantified using a commercially available quantitative sandwich ELISA kit [9].

Statistical Analysis

Statistical analysis was conducted using suitable statistical software. Continuous variables were reported as mean ± SD and range, and categorical variables were reported as numbers and percentages. The Kruskal-Wallis test was used to test for differences in continuous variables between the four Wagner grade groups. The correlation coefficient was used to analyze the correlations between new biomarkers and conventional inflammatory markers. Receiver operating characteristic (ROC) curve analysis was performed to assess the accuracy of the biomarker to predict adverse outcomes, obtaining the AUC. Univariate logistic regression analysis was conducted to estimate the OR and 95% CI of the predictors of burden outcomes.

RESULTS

There was a significant increase in the values of fasting blood glucose, WBC count, ESR, CRP, procalcitonin, and creatinine as the Wagner grade severity increased from Groups 1 to 4 ($p < 0.001$). Crucially, the levels of the novel biomarkers, namely, presepsin, MR-proADM, and endocan, also demonstrated a highly significant, progressive elevation corresponding to the severity of the diabetic foot lesions across the four groups ($p < 0.001$). Presepsin levels increased from 109.30 ± 33.37 pg/mL in Group 1 to 962.97 ± 224.41 pg/mL in Group 4, representing an approximate nine-fold increase. Similarly, MR-proADM concentrations increased from 0.42 ± 0.14 nmol/L to 3.01 ± 0.49 nmol/L, and endocan levels increased from 0.65 ± 0.16 ng/mL to 5.64 ± 0.84 ng/mL across the same groups.

Table 1: Clinical Characteristics and Biomarker Levels by Wagner Grade Groups.

Parameters	Group 1 (n=30) Mean ± SD (Range)	Group 2 (n=30) Mean ± SD (Range)	Group 3 (n=30) Mean ± SD (Range)	Group 4 (n=30) Mean ± SD (Range)	p-value
Age (years)	47.27 ± 9.02 (31.00 - 61.00)	49.93 ± 7.45 (37.00 - 62.00)	49.13 ± 8.70 (34.00 - 62.00)	49.07 ± 7.35 (38.00 - 70.00)	> 0.05
BMI (kg/m²)	25.85 ± 1.70 (23.20 - 28.80)	25.56 ± 1.69 (23.20 - 28.90)	25.30 ± 1.51 (23.40 - 28.40)	25.47 ± 1.35 (23.50 - 28.50)	> 0.05
Duration of DM (years)	6.27 ± 2.15 (3.00 - 10.00)	9.57 ± 2.92 (5.00 - 15.00)	14.10 ± 3.99 (8.00 - 19.00)	17.63 ± 3.85 (10.00 - 25.00)	> 0.05
FBG (mg/dL)	152.34 ± 21.30 (111.10 - 179.3)	175.44 ± 25.95 (132.70 - 212.2)	205.46 ± 30.36 (152.8-257.30)	229.50 ± 39.80 (172.00 - 301.60)	< 0.001***
HbA1c (%)	7.04 ± 0.76 (6.10 - 8.20)	7.05 ± 0.67 (6.10 - 8.20)	7.09 ± 0.62 (6.09 - 8.30)	7.07 ± 0.62 (6.03 - 8.40)	> 0.05
WBC (×10³/µL)	7.44 ± 1.41 (4.70 - 9.40)	9.95 ± 1.62 (7.10 - 12.00)	12.97 ± 1.58 (10.10 - 15.70)	17.00 ± 2.64 (13.40 - 21.80)	< 0.001***
ESR (mm/hr)	14.97 ± 4.77 (9.00 - 24.00)	33.47 ± 7.18 (21.00 - 47.00)	60.97 ± 13.96 (44.00 - 84.00)	88.17 ± 16.74 (63.00 - 119.00)	< 0.001***
CRP (mg/L)	4.92 ± 1.93 (2.10 - 7.80)	24.58 ± 7.25 (10.30 - 34.80)	54.06 ± 16.51 (32.90 - 79.30)	105.77 ± 30.77 (61.00 - 149.40)	< 0.001***

Parameters	Group 1 (n=30) Mean ± SD (Range)	Group 2 (n=30) Mean ± SD (Range)	Group 3 (n=30) Mean ± SD (Range)	Group 4 (n=30) Mean ± SD (Range)	p-value
Procalcitonin (ng/mL)	0.06 ± 0.02 (0.03 - 0.10)	0.31 ± 0.12 (0.11 - 0.48)	1.62 ± 0.55 (0.54 - 2.39)	5.98 ± 2.22 (2.04 - 9.88)	< 0.001***
Creatinine (mg/dL)	0.92 ± 0.15 (0.71 - 1.20)	1.03 ± 0.18 (0.81 - 1.34)	1.33 ± 0.24 (0.92 - 1.75)	1.71 ± 0.47 (1.02 - 2.48)	< 0.001***
Presepsin (pg/mL)	109.30 ± 33.37 (60.30 - 171.20)	143.54 ± 30.70 (90.90 - 190.20)	426.99 ± 47.87 (355.10-530.20)	962.97 ± 224.41 (680.10 - 1330.10)	< 0.001***
MR-proADM (nmol/L)	0.42 ± 0.14 (0.18 - 0.62)	0.98 ± 0.20 (0.61 - 1.31)	1.50 ± 0.20 (1.10 - 1.81)	3.01 ± 0.49 (2.15 - 3.71)	< 0.001***
Endocan (ng/mL)	0.65 ± 0.16 (0.41 - 0.95)	1.86 ± 0.26 (1.43 - 2.29)	3.14 ± 0.69 (2.15 - 4.20)	5.64 ± 0.84 (4.30 - 7.10)	< 0.001***

*Note: Group 1 (Wagner 0), Group 2 (Wagner 1-2), Group 3 (Wagner 3-4), Group 4 (Wagner 4-5). ***p<0.001 indicates significant difference. Kruskal-Wallis*

Table 2, which presents the levels of biomarkers by clinical outcomes. The findings showed that patients with poor outcomes, in particular those with major amputation and death, had substantially elevated levels of all three biomarkers compared to those with wound healing. In comparison, the presepsin levels were 183.09 ± 129.2 pg/mL and 987.70 ± 266.12 pg/mL in the healed and death groups, respectively. Corroborating this, MR-proADM increased from 0.80 ± 0.43 nmol/L to 2.84 ± 0.47 nmol/L and endocan from 1.55 ± 1.04 ng/mL to 5.98 ± 0.71 ng/mL in the healed and death groups, respectively.

Table 2: Biomarker Levels According to Clinical Outcomes.

Biomarkers	Healed (n=65) Mean ± SD	Chronic wound (n=19) Mean ± SD	Minor amputation (n=21) Mean ± SD	Major amputation (n=10) Mean ± SD	Death (n=5) Mean ± SD	p-value
Presepsin (pg/mL)	183.09 ± 129.2	467.97 ± 367.3	654.65 ± 307.6	980.58 ± 195.78	987.70 ± 266.12	< 0.001***
MR-proADM (nmol/L)	0.80 ± 0.43	1.79 ± 0.92	2.25 ± 0.88	2.95 ± 0.51	2.84 ± 0.47	< 0.001***
Endocan (ng/mL)	1.55 ± 1.04	3.32 ± 1.76	4.39 ± 1.52	5.24 ± 0.69	5.98 ± 0.71	< 0.001***

The Spearman rank correlation matrix for the novel biomarkers, classical inflammatory markers, and Wagner grade is shown in Table 3. Among all the parameters analyzed, a significant ($p<0.001$) and strong positive correlation was found. Endocan had the best correlation with the Wagner grade ($r = 0.938$), followed by MR-proADM ($r = 0.929$) and presepsin ($r = 0.891$). The three novel markers correlated well with each other and with known systemic inflammation markers, including CRP ($r = 0.885–0.918$) and procalcitonin ($r = 0.905–0.933$)

Table 3: Presents the complete Spearman correlation matrix among the three biomarkers and the key inflammatory and metabolic markers.

	Presepsin	MR-proADM	Endocan	CRP	PCT	WBC	ESR	Wagner
Presepsin	1.000	0.898***	0.904***	0.885***	0.905***	0.850***	0.871***	0.891***
MR-proADM	0.898***	1.000	0.919***	0.914***	0.923***	0.875***	0.913***	0.929***
Endocan	0.904***	0.919***	1.000	0.918***	0.933***	0.880***	0.901***	0.938***
CRP	0.885***	0.914***	0.918***	1.000	0.923***	0.863***	0.906***	0.928***
PCT	0.905***	0.923***	0.933***	0.923***	1.000	0.870***	0.925***	0.935***
WBC	0.850***	0.875***	0.880***	0.863***	0.870***	1.000	0.857***	0.881***
ESR	0.871***	0.913***	0.901***	0.906***	0.925***	0.857***	1.000	0.914***
Wagner	0.891***	0.929***	0.938***	0.928***	0.935***	0.881***	0.914***	1.000

****p < 0.001, **p < 0.01, *p < 0.05. Test used: Spearman's rank correlation. PCT = Procalcitonin.*

Table 4 presents the results of the ROC curve analyses for the predictive accuracy of the biomarkers in predicting poor clinical outcomes. All biomarkers had good discriminatory power, with AUCs >0.91. At a cut-off of 2.51 ng/mL, endocan had the greatest singular AUC (0.924), with a sensitivity of 97.2% and specificity of 78.6%. At a cut-off of 1.23 nmol/L, with a specificity of 71.4%, MR-proADM had 100% sensitivity. With a cutoff of 377.3 pg/mL, the AUC of presepsin was 0.915. A combined score including all biomarkers achieved an AUC of 0.923, further validating the strength of these markers as predictors.

Table 4: ROC Curve Analysis for Predicting Adverse Outcomes.

Biomarkers	AUC (95% CI)	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Presepsin (pg/mL)	0.915	377.3	97.2	75.0	62.5	98.4
MR-proADM (nmol/L)	0.920	1.23	100.0	71.4	60.0	100.0
Endocan (ng/mL)	0.924	2.51	97.2	78.6	66.0	98.5
Combined Score	0.923	-0.044	97.2	78.6	66.0	98.5

The results of the regression analysis for adverse outcome prediction are shown in Table 5. All assessed variables were significant predictors ($p < 0.001$). MR-proADM was the best predictor, with more than seven times the risk of adverse outcomes (OR = 7.331; 95% CI: 3.679–14.610). Endocan had a good predictive value (OR = 2.951; 95% CI: 2.044–4.261), as did procalcitonin (OR = 2.246; 95% CI: 1.663–3.032) and WBC count (OR = 1.917; 95% CI: 1.496–2.456). Estimates for CRP (OR = 1.061) and presepsin (OR = 1.006) were also significant, albeit with a modest odds ratio of the latter due to the fact that it is measured in smaller units (pg/mL).

Table 5: Univariate Logistic Regression for Adverse Outcomes.

Predictor	Odds Ratio	95% CI	p-value
Presepsin (pg/mL)	1.006	1.004 - 1.008	< 0.001
MR-proADM (nmol/L)	7.331	3.679 - 14.610	< 0.001
Endocan (ng/mL)	2.951	2.044 - 4.261	< 0.001
WBC (×10³/µL)	1.917	1.496 - 2.456	< 0.001
CRP (mg/L)	1.061	1.039 - 1.084	< 0.001
Procalcitonin (ng/mL)	2.246	1.663 - 3.032	< 0.001

DISCUSION

This study from the Middle East indicates that presepsin, MR-proADM, and endocan levels were markedly increased in patients with severe diabetic foot problems, and these three molecules were powerful and independent predictors of poor clinical outcomes, including major amputation and death. The progressive increase in these biomarkers with advancing Wagner grades not only underscores their applicability in detecting infection but also attests to their use as markers for severe tissue damage, severe endothelial dysfunction, and systemic physiological derangement.

Our findings on presepsin levels are consistent with recent reports that presepsin is a superior diagnostic and prognostic marker for severe infectious diseases. Baspinar et al., b: AUC 0.829 at the cut-off of 1020 pg/mL; a prospective observational study that included presepsin levels was markedly increase in patients with severe DFU requiring amputation and was superior to conventional markers such as CRP and PCT [5].

Our findings showed that presepsin had a better AUC (0.915) for the lower cut-off (377.3 pg/mL) because the concept of a 'poor outcome' was extended not only to amputation but also to death. In addition, Alkhawaja et al. have proven that presepsin can predict the early development of severe infection amputation in diabetic foot ulcer patients, with a good correlation to the Wagner classification grade [12]. These results are consistent with our correlational findings (r = 0.891, p < 0.001).

The biological basis for the superiority of presepsin is related to its mechanism of secretion. This clearly shows that presepsin is not simply an acute-phase reactant such as CRP and PCT but is a sepsis-specific protein that is produced through bacterial phagocytosis by monocytes and macrophages [6] [13]. A recent meta-analysis by Xing et al. . including 2,066 patients, confirmed that presepsin is a valuable prognostic marker in sepsis and septic shock and showed stable predictive performance in different disease severities [14]. Likewise, Peng et al. conducted a meta-analysis and found that presepsin is an excellent and one of the most promising biomarkers for sepsis diagnosis (general and pediatric populations) with good diagnostic accuracy [15]. The nearly ninefold increase in presepsin levels between our least and most severely ill patients emphasizes that it has the power to mirror the systemic load of the localized ulcer as it migrates from a room-contained wound to a systemic bacteremia origin.

The significant predictive value of MR-proADM in our results (OR = 7.331) further highlights its established role as a biomarker of microcirculatory failure and organ dysfunction. MR-proADM is a stable fragment of adrenomedullin, a strong vasodilator that is increased during hypoxic and inflammatory conditions to maintain endothelial integrity [7] [8]. Valenzuela-Sánchez et al. demonstrated that MR-proADM the severity

of organ failure and should be considered for inclusion in biomarker panels for the diagnosis and prognosis of sepsis [8]. A recent study by Spoto et al. reported that MR-proADM has high predictiveness in severe inflammation, such as sepsis and acute heart failure [16]. They also showed that MR-proADM could predict organ failure more accurately than conventional markers [16].

In particular, our findings are well aligned with the study by Mohammedi et al. was the first to assess this association in two large cohorts of patients with type 2 diabetes (n = 4,375), revealing that increased plasma levels of MR-proADM were independently related to the heightened risk of lower-limb amputation [17]. This finding provides direct proof of a link between adrenomedullin pathways and limb loss in individuals with diabetes. In our group, MR-proADM concentrations in deceased patients (2.84 0.47 nmol/L) were more than three times higher than those in patients who healed (0.80 0.43 nmol/L), indicating extensive, irrecoverable ischemic tissue injury and imminent systemic breakdown. A review conducted by Fialek et al. reconfirmed that MR-proADM concentration in the non-survivors of critical illness was roughly twice as high as that in the survivors (1.692 vs. A further meta-analysis, conducted by Baldirà et al., established midregional-proAdrenomedullin as a dependable prognostic marker in sepsis, with high concentrations being uniform indicators of death [18].

The positive association between endocan levels and DFU severity offers important information on the potential role of endothelial dysfunction in diabetic complications. Endocan is a soluble proteoglycan that is secreted specifically by the activated vascular endothelium and participates in the control of inflammatory cell recruitment and angiogenesis [9]. A review and meta-analysis of 24 studies (3,354 cases) by Khalaji et al. reported that serum endocan levels were significantly increased in patients with diabetes compared to healthy individuals (SMD 1.00, 95% CI 0.81–1.19, $p < 0.01$), and higher levels in chronic diabetes complications (retinopathy, nephropathy, and peripheral neuropathy) were also reported [10]. Our findings go a step further, demonstrating that endocan is not only highly correlated with the Wagner grade (r=0.938) but also excellently predicts adverse outcomes (AUC=0.924).

Jena et al. further showed that endocan expression is markedly increased in diabetic peripheral neuropathy and is associated with other endothelial markers, confirming its application as an indicator of endothelial dysfunction in diabetic microvascular disease [9]. The dramatic increase in circulating endocan levels in our patients with chronic non-healing wounds and amputations indicates that extreme and enduring endothelial damage may be a key mechanism of impaired wound healing and tissue loss in DFU. Scierka et al. reported that endocan is a good of sepsis severity that is comparable to SOFA and APACHE II scores [19]. Furthermore, Zolali et al. revealed that endocan production is increased in diabetic conditions in human endothelial cells, thereby associating hyperglycemia-mediated endothelial dysfunction with impaired wound healing and the pathogenesis of diabetic foot ulcers [20].

The high degree of inter-correlation between presepsin, MR-proADM, and endocan (r = 0.898–0.919) indicates that the pathogenesis of severe DFU is a concerted cascade driven by bacterial invasion, microcirculatory disturbance, and significant endothelial damage. Although conventional markers such as WBC and CRP are still valuable, the combination of these novel markers provides an overall pathophysiological view. Farine et al. noted that although WBC, CRP, and PCT are useful in predicting amputation, they are nonspecific

markers, and there is a need for novel biomarkers for better risk stratification [21]. Our combined biomarker score had an AUC of 0.923, similar to the finding of Okiro et al.(2026) that combined biomarker panels provide better AUC for predicting outcomes in DFU than single markers [22].

The excellent sensitivity (97.2%) and specificity (78.6%) observed in the ROC curve suggest that the use of these biomarkers, either alone or in the form of a composite score, could substantially improve clinical evaluation. Clinicians can expedite aggressive surgical debridement, targeted antimicrobial therapy, and revascularization procedures by recognizing patients at the greatest risk for amputation or death upon admission. This strategy dovetails with the present focus on multidisciplinary management of diabetic foot disease, which has been correlated with reduced major amputation rates [1].

Limitations

This study has a few limitations that should be addressed. The similarity of the included studies and the (relatively small) sample size (n = 120). In addition, biomarkers assessed cross-sectionally at admission to treatment do not capture dynamic alterations in these markers during treatment; therefore, future multicenter, longitudinal studies with serial biomarker assessments are needed to confirm these results and establish final cut-off values for application in clinical practice.

CONCLUSION

The combination of new markers, namely, presepsin, MR-proADM, and endocan, allows for a very good synergistic prediction of complications in patients with DFUs. Instead of being only a sign of infection, these markers are combined expressions of the extent of tissue necrosis, endothelial dysfunction, and system-wide physiological derangement. They have superior predictive ability with respect to major amputation and mortality compared to conventional inflammatory markers; therefore, this biomarker panel may be a key tool for early risk stratification in routine clinical settings. Ultimately, this precision-guided strategy may allow for earlier focused therapeutic measures and reduce the devastating morbidity and mortality of diabetic foot disease.

Declaration

Funding:

None.

Conflicts of Interest:

None.

Ethical Approval:

The study was conducted in conformity with the Declaration of Helsinki and was approved by the Institutional Ethics Committee. Prudent consent for the study was provided by all participants.

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