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Original Article

Combined PDGF and ANGPTL4 in diabetic foot: diagnostic value and exploratory early changes after plantar arch angioplasty plus alprostadil

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Abstract: Objective: To evaluate the diagnostic value of combined platelet-derived growth factor (PDGF) and angiopoietin-like protein 4 (ANGPTL4) for distinguishing diabetic foot (DF) from diabetes mellitus (DM) without DF, and to explore their early changes following treatment initiation and their associations with 3-month ulcer healing. Methods: Clinical data were retrospectively collected from January 2024 to May 2025. Before propensity score matching (PSM), 153 patients with DF and 116 non-DF DM patients met the eligibility criteria; after 1:1 PSM, 97 patients were retained in each group. Serum PDGF and ANGPTL4 were measured at baseline in both groups, with additional measurements taken on day 5 after the initiation of plantar arch angioplasty (PAA) and alprostadil in the DF group. The primary analysis evaluated the diagnostic performance of the baseline biomarkers using receiver operating characteristic (ROC) curves, while secondary exploratory analyses assessed their day-5 changes and associations with 3-month ulcer healing. Results: At baseline, PDGF was 26.23% lower and ANGPTL4 was 32.22% higher in the DF group than in the matched DM group (both $P<0.05$). The combined baseline model yielded an area under the curve (AUC) of 0.805, surpassing the performance of either biomarker alone. Both biomarkers were also associated with ulcer size, Wagner grade, fasting plasma glucose, and hemoglobin A1c. On day 5 after PAA and alprostadil initiation, PDGF significantly increased and ANGPTL4 significantly decreased relative to baseline (both $P<0.05$). At 3 months, 66 of 97 patients achieved complete ulcer healing; the combined day-5 model discriminated healing status with an AUC of 0.764, a sensitivity of 59.09%, and a specificity of 87.10%. Conclusion: The combination of baseline PDGF and ANGPTL4 improved DF discrimination compared with either biomarker alone. Their day-5 changes and associations with 3-month ulcer healing were exploratory and should not be interpreted as evidence of treatment efficacy or validated prognostic utility.

Keywords: Diabetic foot, PDGF, ANGPTL4, diagnostic biomarkers, plantar arch angioplasty

Introduction

Diabetic foot (DF) affects approximately 15-25% of adults with diabetes during their lifetime and represents a serious chronic complication that may progress to ulceration or gangrene [1]. Prolonged hyperglycemia contributes to peripheral neuropathy, vascular injury, and immune dysfunction, thereby promoting lower-limb ischemia, infection, and tissue necrosis [2]. Although fasting plasma glucose (FPG) is routinely used to assess glycemic status [3], it value in identifying DF or characterizing ulcer progression is limited [4]; thus, more reliable and clinically accessible biomarkers are needed to complement standard clinical assessment.

Platelet-derived growth factor (PDGF) is a key mediator of angiogenesis and tissue repair. It stimulates granulation tissue formation and promotes fibroblast and smooth muscle cells proliferation and migration, thereby accelerating wound healing [5]. In contrast, angiopoietin-like protein 4 (ANGPTL4) protects against ischemia-reperfusion injury by modulating lipid metabolism, reducing inflammatory cytokine release, and improving endothelial barrier func-

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tion [6]. Given these distinct biological functions, PDGF and ANGPTL4 may provide complementary insights into DF pathophysiology. A recent cellular study also suggested an interaction between ANGPTL4 and PDGF-related signaling in vascular smooth muscle cells [7], supporting the rationale for evaluating these two biomarkers in combination.

Despite their biological plausibility, evidence regarding circulating PDGF and ANGPTL4 in DF remains limited. The primary objective of this retrospective matched study was to determine whether baseline PDGF and ANGPTL4, individually and jointly, could distinguish patients with DF from patients with DM without DF. The secondary objectives were exploratory: to describe their day-5 changes following PAA and alprostadil initiation, and to examine their associations with complete ulcer healing at 3 months. As no control group receiving alternative treatment was included, these analyses were not intended to establish treatment efficacy.

Materials and methods

Research design

This retrospective, single-center observational study included patients with type 2 diabetes mellitus (T2DM) treated at our hospital between January 2024 and May 2025. Propensity score matching (PSM) was performed to construct cohorts for the primary comparison of baseline biomarker levels, while secondary analyses within the matched groups evaluated day-5 biomarker changes and their associations with 3-month ulcer healing. Owing to the retrospective design, the requirement for written informed consent was waived, and all patient data were anonymized prior to analysis.

Data acquisition

Clinical data, laboratory results, imaging data, and follow-up information were extracted from the hospital's electronic medical record system (EMR), laboratory information system (LIS), and picture archiving and communication system (PACS). Data extraction was performed independently by two trained researchers, who subsequently cross-verified each other's work. Any disagreements in data extraction were resolved through consultation with a senior clinician, ensuring completeness and accuracy of the study data. Safety data during the 14-day alprostadil course, including injection-site reactions, gastrointestinal symptoms, flushing, headache, hypotension, bleeding events, treatment discontinuation, and serious adverse events, were extracted from inpatient progress notes, nursing records, and medication records.

Inclusion and exclusion criteria

Inclusion criteria for DF group: 1) A confirmed diagnosis of DM, defined as FPG ≥7.0 mmol/L, 2-hour postprandial blood glucose ≥11.1 mmol/L, or HbA1c ≥6.5% [8]; 2) Presence of foot ulcers or gangrene, with signs of neuropathy and/or vasculopathy; 3) A Wagner grade [9] between 1 and 5; and 4) Age ≥40 years and diabetes course ≥1 year. Inclusion criteria for DM group: ① A confirmed diagnosis of DM; ② Absence of foot ulcers, gangrene, or signs of lower-extremity ischemia (e.g., rest pain); and ③ Matching the DF group in age (within 5 years) and diabetes course (within 1 year). Exclusion criteria: ① Significant vascular pathologies, including prior coronary stenting, recent cerebrovascular accidents, or peripheral artery bypass procedures; ② Severe hepatic or renal dysfunction; ③ Any active malignancy or a cancer diagnosis within the preceding five years; ④ Pregnancy or lactation; and ⑤ Administration of medications influencing angiogenesis within the past month.

PSM

Before PSM, 153 patients with DF and 116 patients with DM without DF met the eligibility criteria. Propensity scores were estimated using age, sex, diabetes duration, body mass index (BMI), smoking status, alcohol use, and hypertension. A 1:1 nearest-neighbor matching was performed with a caliper of 0.2 standard deviations of the logit of the propensity score, yielding 97 matched pairs and a final cohort of 194 patients. Post-matching covariate balance was assessed using standardized mean differences (SMDs).

Intervention and management

All DF patients underwent plantar arch angioplasty (PAA) performed by the same surgical team, followed by 14 days of intravenous alprostadil at a dose of 10 μg/day diluted in

100 mL of normal saline. Ulcer healing was assessed at 3 months after surgery, with complete healing defined as full epithelialization of the index ulcer without drainage, active infection, exposed deep tissue, or the need for additional debridement, repeat revascularization, amputation, or other ulcer-directed interventions. Healing status was reviewed from outpatient records and wound photographs by two trained investigators who were blinded to serum PDGF and ANGPTL4 results and were not involved in patient treatment; formal treatment-blinded adjudication was not feasible because of the retrospective design.

Outcome measurements

Serum levels of nitric oxide (NO), platelet-derived growth factor (PDGF), angiopoietin-like protein 4 (ANGPTL4), endothelin-1 (ET-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF), and transforming growth factor-β1 (TGF-β1) were measured using enzyme-linked immunosorbent assay (ELISA) with kits provided by Beijing Biosynthesis Biotechnology Co., Ltd., according to the manufacturer's instructions. FPG and HbA1c levels were determined using a Roche fully automated biochemistry analyzer. The toe-brachial index (TBI) and the ankle-brachial index (ABI) were measured using a Doppler blood flow detector. Patients were instructed to rest in the supine position for 10 minutes before the systolic pressures of the toe artery, posterior tibial artery, and dorsalis pedis artery were sequentially measured. Standard clinical formulas were subsequently used to calculate ABI and TBI. Transcutaneous oxygen pressure ($TcPO_2$) was assessed at the plantar lesion site using a transcutaneous oxygen monitor. The value was recorded after the reading had stabilized with the sensor placed over the lesion. Skin temperature around the plantar lesion was measured using an infrared skin thermometer, with the measurement point chosen at the center of the lesion. Three readings were taken and averaged. Foot pain intensity was evaluated using the visual analogue scale (VAS) [10], ranging from 0 (no pain) to 10 (severe pain).

Statistical analysis

Statistical analyses and graphical presentations were performed using GraphPad Prism 8. Differences in categorical data [n (%)] between groups were compared using the chi-square test. Continuous variables were first assessed for normality using Shapiro-Wilk test. All data conformed to normal distribution and were presented as mean ± standard deviation (SD). Between-group comparisons were performed using the independent-samples t-test, while within-group comparisons were conducted using the paired t-test.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of baseline biomarkers to distinguish DF from DM without DF, with the areas under the curve (AUCs) calculated. In addition, the discriminative ability of day-5 biomarker levels for 3-month ulcer-healing status was evaluated using ROC curve analysis; optimal cutoffs were selected using the Youden index and were considered exploratory. Multivariable logistic regression was used to construct the combined biomarker models, and Pearson correlation coefficients were calculated to assess associations between continuous variables. A two-sided *P*-value <0.05 was considered statistically significant.

Results

Participant selection and baseline characteristics

Before PSM, 153 DF patients and 116 non-DF DM patients met the eligibility criteria. After 1:1 matching, 97 pairs of patients were retained. The distributions of the matched covariates and their corresponding SMDs are presented in **Table 1**. Notably, FPG and HbA1c were significantly higher in the DF group than in the DM group (**Table 1**).

Primary analysis: diagnostic performance of baseline PDGF and ANGPTL4

At baseline, the DF group exhibited lower PDGF levels and higher ANGPTL4 levels than the matched DM group (both P<0.05). Individually, PDGF and ANGPTL4 discriminated DF from DM without DF, with AUCs of 0.758 and 0.744, respectively, whereas the combined model yielded an AUC of 0.805, a sensitivity of 77.32%, and a specificity of 72.16% (**Figure 1**; **Table 2**). The exploratory diagnostic cutoffs

Table 1. Comparison of baseline clinical data between the DM and DF groups

	DM patients (n=97)	DF patients (n=97)	χ^2 (or t)-values	*P*-values	SMD
Age	68.45±5.85	69.34±6.62	0.988	0.324	-0.142
Male/female	42/55	46/51	0.333	0.564	-0.083
Duration of DM (years)	6.00±2.75	5.95±2.16	0.145	0.885	0.020
BMI (kg/m^2)	23.12±3.14	23.74±2.69	1.467	0.144	-0.212
Smoking history (yes/no)	40/57	47/50	1.021	0.312	-0.145
Alcohol consumption (yes/no)	34/63	42/55	1.384	0.239	-0.170
Combined hypertension (yes/no)	28/69	34/63	0.853	0.356	-0.133
FPG (mmol/L)	8.72±1.17	11.73±2.32	11.394	<0.001	-
HbA1c (%)	7.90±0.79	9.79±1.29	12.341	<0.001	-

Note: DM, diabetes mellitus; DF, diabetic foot; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; SMD, standardized mean difference; χ^2, chi-square.

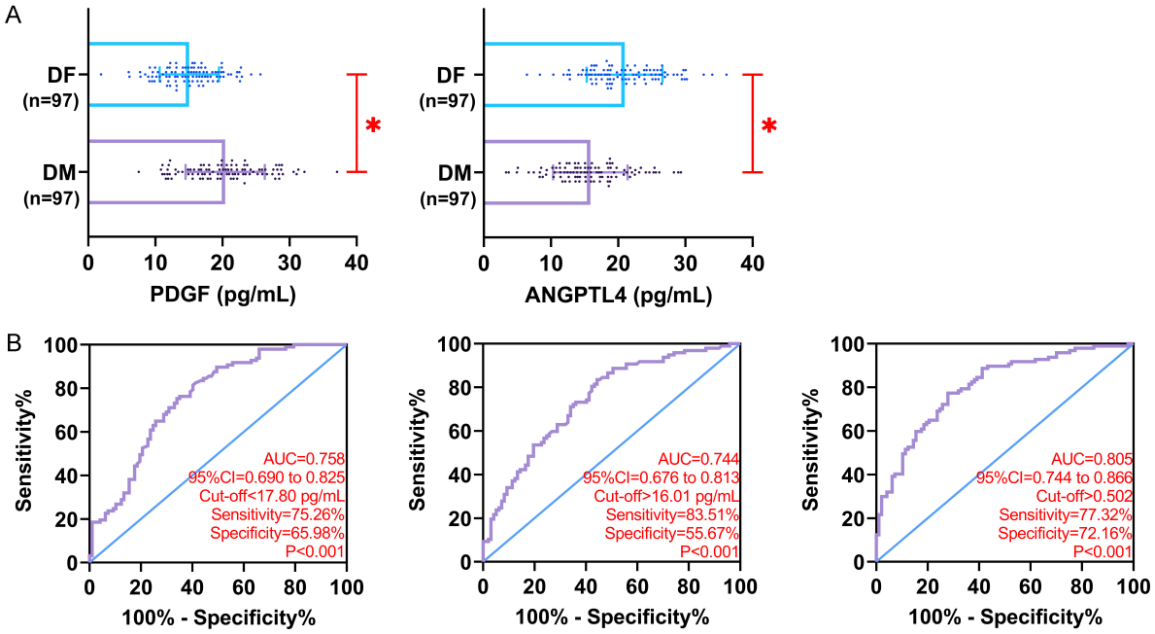

Figure 1. Baseline serum PDGF and ANGPTL4 levels and their diagnostic performance for distinguishing DF from DM without DF. A. Comparison of PDGF and ANGPTL4 levels between DM patients with and without DF; B. ROC analysis of PDGF, ANGPTL4, and their combination for differentiating DF from DM. Notes: *P<0.05. PDGF, platelet-derived growth factor; ANGPTL4, angiopoietin-like protein 4; DM, diabetes mellitus; DF, diabetic foot; ROC, receiver operating characteristic.

were PDGF <17.80 pg/mL, ANGPTL4 >16.01 pg/mL, and a combined-model probability >0.502.

Associations of PDGF and ANGPTL4 with DF severity

Stratification by Wagner grade revealed that patients with mild DF (Wagner grades 1-3, n=52) had significantly higher PDGF levels and lower ANGPTL4 levels than patients with severe DF (Wagner grades 4-5, n=45) (P<0.05). Similarly, with smaller ulcers (n=50) exhibited higher PDGF levels and lower ANGPTL4 levels than those with larger ulcers (both P<0.05). Correlation analyses further showed that PDGF levels were negatively correlated with FPG and HbA1c, whereas ANGPTL4 levels were positively correlated with these parameters (P< 0.05) (**Figure 2**).

Table 2. Multivariate logistic regression analysis of combined PDGF and ANGPTL4 for distinguishing DF from DM without DF

	B	S.E.	Wald	P	OR	95% CI
PDGF	-0.164	0.037	19.924	<0.001	0.849	0.790-0.912
ANGPTL4	0.122	0.033	13.611	<0.001	1.130	1.059-1.205
Constant	0.699	0.951	0.496	0.481	-	-

Note: PDGF, platelet-derived growth factor; ANGPTL4, angiopoietin-like protein 4; DF, diabetic foot; DM, diabetes mellitus; B, regression coefficient; S.E., standard error; Wald, Wald statistic; OR, odds ratio; CI, confidence interval.

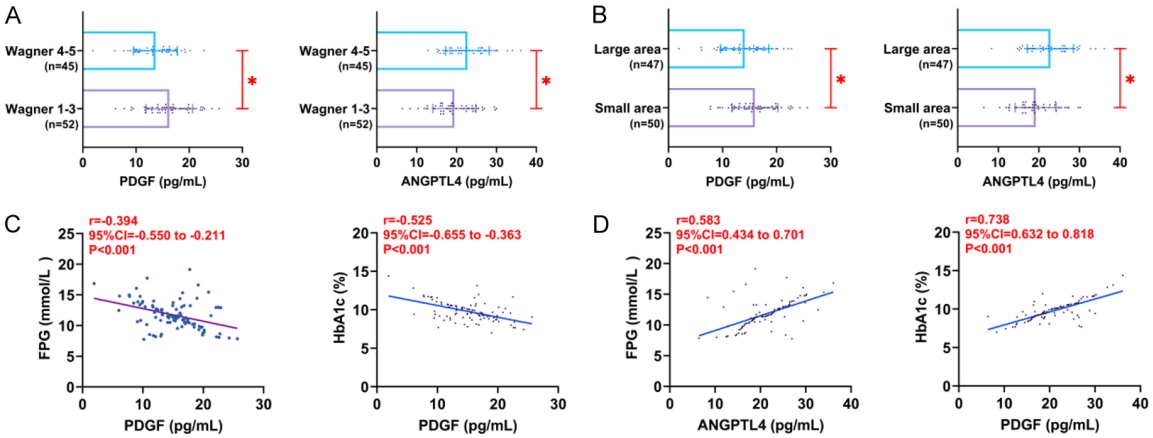

Figure 2. Stratified analysis of PDGF and ANGPTL4 by DF severity and their correlations with glycemic control. A. Comparison of serum PDGF and ANGPTL4 levels between patients with Wagner grades 1-3 and Wagner grades 4-5. B. Comparison of serum PDGF and ANGPTL4 levels between patients with smaller ulcers and larger ulcers. C. Pearson correlations between PDGF and FPG (left) and HbA1c (right). D. Pearson correlations between ANGPTL4 and FPG (left) and HbA1c (right). Notes: *P<0.05. PDGF, platelet-derived growth factor; ANGPTL4, angiopoietin-like protein 4; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; DF, diabetic foot.

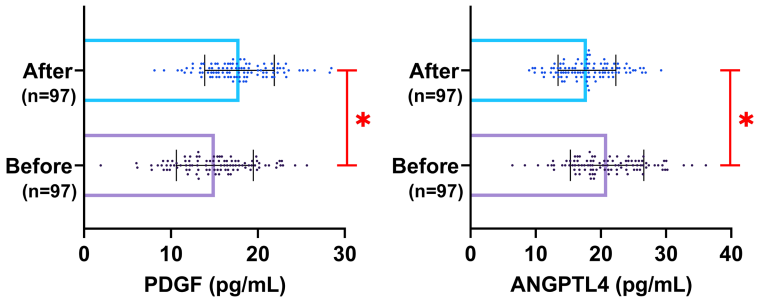

Figure 3. Changes in serum PDGF and ANGPTL4 levels from baseline to day 5 after PAA and alprostadil initiation. Notes: *P<0.05. PDGF, platelet-derived growth factor; ANGPTL4, angiopoietin-like protein 4; PAA, plantar arch angioplasty.

Secondary exploratory analysis: day-5 changes in PDGF and ANGPTL4

On day 5 after PAA and alprostadil initiation, PDGF levels were significantly higher and ANGPTL4 levels were 14.78% lower than at baseline (P<0.05; **Figure 3**).

Secondary exploratory analysis: PDGF, ANGPTL4, and 3-month ulcer healing

At the predefined 3-month assessment, complete ulcer healing was observed in 66 of 97 DF patients, corresponding to a healing rate of 68.04%. Day-5 PDGF levels were higher and ANGPTL4 levels were lower in patients whose ulcers healed than in those whose ulcers remained unhealed (both P<0.05). Individually, PDGF and ANGPTL4 discriminated 3-month ulcer-healing status with AUCs of 0.692 and 0.697, respectively, whereas the combined model yielded an AUC of 0.764, a sensitivity of 59.09%, and a specificity of 87.10% (P<0.05). Given its limited sensitivity, the combined model should not be used as a

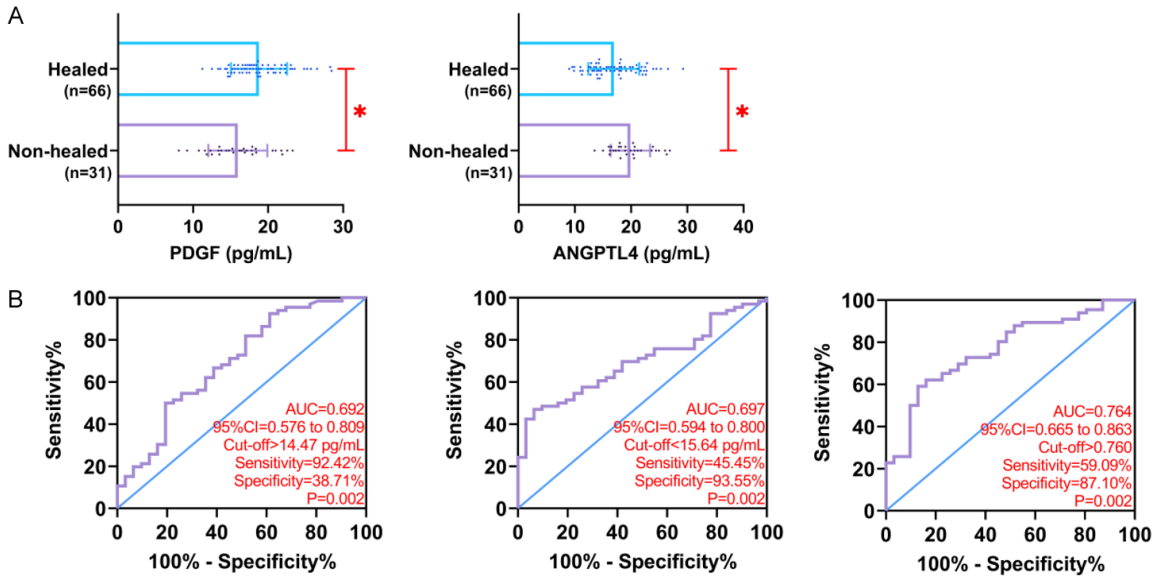

Figure 4. Association of day-5 PDGF and ANGPTL4 levels with 3-month ulcer healing and their predictive performance. A. Comparison of day-5 serum PDGF and ANGPTL4 levels between patients with healed and unhealed ulcers at 3 months. B. ROC curves of day-5 PDGF, ANGPTL4, and their combined model for predicting 3-month ulcer healing status. Notes: *P<0.05. PDGF, platelet-derived growth factor; ANGPTL4, angiopoietin-like protein 4; ROC, receiver operating characteristic.

Table 3. Multivariate logistic regression analysis of combined PDGF and ANGPTL4 for predicting non-healing ulcers in DF patients after treatment

	B	S.E.	Wald	P	OR	95% CI
PDGF	0.201	0.070	8.151	0.004	1.222	1.065-1.406
ANGPTL4	-0.156	0.059	7.078	0.008	0.856	0.763-0.960
Constant	0.117	1.596	0.005	0.942	-	-

Note: PDGF, platelet-derived growth factor; ANGPTL4, angiopoietin-like protein 4; DF, diabetic foot; B, regression coefficient; S.E., standard error; Wald, Wald statistic; OR, odds ratio; CI, confidence interval.

stand-alone clinical tool; rather, these biomarkers should be interpreted in conjunction with wound characteristics, perfusion indices, infection assessment, and standard clinical grading systems (**Figure 4**; **Table 3**).

Changes in vascular endothelial function and lower-extremity blood perfusion indices

At baseline, the DF group had lower serum NO, ABI, TBI, plantar $TcPO_2$, and skin temperature, along with higher ET-1 and VAS pain scores, than the DM group (all P<0.05). On day 5 after PAA and alprostadil initiation, NO, ABI, TBI, $TcPO_2$, and skin temperature increased, whereas ET-1 and VAS scores decreased relative to baseline (P<0.05; **Table 4**).

Changes in inflammatory cytokines and wound-healing-related factors and their associations with ulcer healing

Compared with the DM group, the DF group had higher IL-6 and TNF-α and lower VEGF and TGF-β1 at baseline (all P<0.05). On day 5 after PAA and alprostadil initiation, IL-6 and TNF-α decreased and VEGF and TGF-β1 increased relative to baseline, although all four markers remained significantly different from those in the DM group (P<0.05; **Table 5**).

Safety during alprostadil treatment

During the 14-day alprostadil course, no serious adverse events, clinically relevant bleeding, symptomatic hypotension, gastrointestinal

Table 4. Changes in vascular endothelial function and lower-extremity blood perfusion indices in DM and DF patients

	NO (μmol/L)	ET-1 (pg/mL)	ABI	TBI	$TcPO_2$ (mmHg)	Skin temperature (°C)	VAS
DM patients (n=97)	39.43±5.30	59.68±7.79	1.12±0.07	0.80±0.08	-	36.56±0.34	-
DF patients before treatment (n=97)	22.65±4.10*	97.09±12.00*	0.67±0.11*	0.38±0.09*	27.99±4.63	33.81±0.59*	6.39±1.20
DF patients after treatment (n=97)	32.30±3.97*,#	74.33±9.54*,#	0.94±0.19*,#	0.66±0.09*,#	43.86±5.38*,#	35.68±0.41*,#	2.47±0.79*,#

Note: *P<0.05, compared with DM patients, #P<0.05, compared with DF patients before treatment. NO, nitric oxide; ET-1, endothelin-1; ABI, ankle-brachial index; TBI, toe-brachial index; $TcPO_2$, transcutaneous oxygen pressure; VAS, visual analogue scale; DM, diabetes mellitus; DF, diabetic foot.

Table 5. Expression of inflammatory cytokines and wound repair factors in DM and DF patients

	IL-6 (pg/mL)	TNF-α (pg/mL)	VEGF (pg/mL)	TGF-β1 (pg/mL)
DM patients (n=97)	15.57±3.58	12.73±2.97	326.75±44.60	183.13±27.17
DF patients before treatment (n=97)	48.09±10.29*	37.15±7.34*	187.08±34.24*	96.83±19.44*
DF patients after treatment (n=97)	27.36±7.21*,#	21.56±6.27*,#	269.51±40.74*,#	161.46±28.66*,#

Note: *P<0.05, compared with DM patients, #P<0.05, compared with DF patients before treatment. IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; TGF-β1, transforming growth factor-β1; DM, diabetes mellitus; DF, diabetic foot.

symptoms requiring treatment, or treatment discontinuation were recorded were recorded.

Discussion

The principal finding of this study was that baseline PDGF and ANGPTL4 provided complementary information for distinguishing DF from DM without DF, with the combined model achieving an AUC of 0.805. Secondary analyses showed that PDGF increased and ANGPTL4 decreased on day 5 after PAA and alprostadil initiation, while day-5 biomarker levels were associated with 3-month ulcer-healing status. These secondary findings should be interpreted as exploratory, as all patients with DF received the same combined intervention and no treatment comparator was available; consequently, the observed changes cannot establish treatment efficacy or distinguish the respective contributions of PAA and alprostadil.

Previous experimental studies have linked PDGF to angiogenesis, fibroblast proliferation, collagen formation, and MAPK/ERK signaling [11, 12]; however, MAPK/ERK activity was not measured in the present clinical cohort. Our findings revealed significantly lower baseline PDGF concentrations in patients with DF, and these levels correlated with both ulcer size and Wagner grade. The protracted duration of DF ulcers is primarily attributable to the impaired vascular repair mechanisms inherent to the condition. The increase in PDGF observed on day 5 may reflect an early biological response after treatment initiation; however, without a DF comparator group, this temporal change cannot be interpreted as evidence of treatment efficacy. Clinical evidence suggests that PDGF contributes to the proliferation of DF. For example, Cao Z et al. implicated PDGF and its receptor (PDGFR) signaling in numerous diabetes-associated complications [13]. One therapeutic approach demonstrating improved clinical outcomes in DF ulcers involves the combination of platelet-rich fibrin and hyaluronic acid, which modulates PDGF activity [14]. However, the role of ANGPTL4 in diabetes-related diseases has not been extensively investigated.

ANGPTL4 has been associated with lipid metabolism, endothelial regulation, inflammation, and PPARγ-related signaling in previous experimental studies [15]. It may also promote angiogenesis by upregulating VEGF-A expression [16]. In our cohort, DF patients exhibited higher ANGPTL4 levels, which were positively correlated with both FPG and HbA1c. This finding indicates an association between poorer glycemic control and higher ANGPTL4 levels, but does not prove that hyperglycemia directly induces ANGPTL4 expression; reverse causality and residual confounding related to ulcer severity, infection, ischemia, renal function, or prior treatment exposure cannot be excluded. In addition, a previous study [17] found that ANGPTL4 protects against diabetic nephropathy, which indirectly supports our findings. In vitro studies by He W et al. showed that ANGPTL4 inhibits PDGF-induced smooth muscle cell proliferation by competing with PDGFR-β for binding sites [7]. This mechanism may partly explain the complementary diagnostic performance of the two markers, although this interpretation remains hypothesis-generating, because pathway-level assays were not performed in this study.

Combining PDGF and ANGPTL4 improved the discrimination between DF and DM without DF, increasing the AUC to 0.805 compared with 0.758 and 0.744 for the individual biomarkers. This complementary use of circulating biomarkers aligns with multimarker approaches applied in other clinical settings [18], although direct comparisons across diseases should be made cautiously. The day-5 combined model also discriminated 3-month ulcer-healing status with an AUC of 0.764; however, its sensitivity was only 59.09%, and the exploratory model requires independent validation before it can be considered for clinical use. Serum biomarker assays offer advantages over conventional imaging modalities, including non-invasiveness, low cost, and ease of repeat administration, making them particularly suitable for primary care and long-term follow-up. Serial PDGF and ANGPTL4 measurements may eventually complement wound examination, perfusion indices, infection assessment, and Wagner grading; however, the present retrospective findings do not support the use of biomarker thresholds to guide clinical decision-making, such as anti-infective treatment, repeat vascular intervention, stem-cell therapy, or other treatment escalation. Prospective studies are needed to determine whether repeated biomarker mea-

surement provides clinically useful information beyond established wound and vascular assessments. Our findings suggest that PDGF and ANGPTL4 play important roles in the pathophysiology of DF, raising the possibility that future studies may develop novel targeted therapies. This could entail the development of ANGPTL4 inhibitors or PDGF mimetics aimed at precisely regulating the equilibrium between vascular repair and inflammatory responses to improve patient prognosis.

Assessment of vascular endothelial and blood perfusion indices also showed that patients with DF had higher ET-1 levels and lower serum NO levels before treatment. The ABI, TBI, plantar $TcPO_2$, and skin temperature readings were all abnormal, and the VAS pain scores were significantly elevated. Similar findings have been seen in other studies, which suggest that chronic hyperglycemia disrupts vascular endothelial regulation, compromising lower-extremity circulation, including the most distal regions, thereby contributing to DF pathogenesis [19]. Following the combined therapeutic interventions, these parameters showed marked improvement. At the anatomical level, PAA facilitates the restoration of blood circulation to the plantar region, thereby restoring blood flow to the lower extremities [20]. At the functional level, alprostadil offers endothelial protection and induces relaxation of vascular smooth muscle [21]. Patients with DF and lower-extremity ischemia and associated foot pain may benefit from this combined therapeutic intervention. Regarding inflammatory and wound-repair markers, those with DF presented with elevated IL-6 and TNF-α levels and reduced VEGF and TGF-β1 levels before treatment initiation. These observations align with existing evidence that chronic inflammation hampers the healing process of DF ulcers, while insufficient repair factors at the wound site directly compromise angiogenesis and tissue repair [22]. After combined treatment, levels of repair factors increased and inflammatory cytokine levels decreased. One possible mechanism is that alprostadil suppresses the release of pro-inflammatory mediators, thereby breaking the local "inflammation-injury" cycle [23]. Concurrently, improved blood flow alleviates local ischemia and hypoxia, promoting endogenous repair factor production [24].

This study has several limitations. First, it was a single-center retrospective analysis with 97 matched participants in each group, which may limit the generalizability of the findings. Second, all patients with DF received PAA plus alprostadil, and no DF comparator group received PAA alone, alprostadil alone, or standard care; therefore, the observed biomarker changes cannot be attributed to the combined intervention or to either treatment component individually. Third, follow-up was limited to 3 months, precluding evaluation of longer-term healing, ulcer recurrence, and amputation outcomes. Finally, PDGF and ANGPTL4 were measured by ELISA without confirmation using an independent analytical method. Larger prospective multicenter studies with appropriate comparator groups are needed to validate the diagnostic findings and clarify the clinical significance of the early biomarker changes.

Conclusion

In this retrospective PSM cohort, the combination of baseline PDGF and ANGPTL4 discriminated DF from DM without DF more effectively than either biomarker alone. PDGF increased and ANGPTL4 decreased on day 5 after PAA and alprostadil initiation, and day-5 levels were associated with 3-month ulcer-healing status. However, these secondary findings were exploratory and should not be interpreted as evidence of treatment efficacy or validated prognostic utility. Prospective multicenter studies are required to validate the diagnostic model and to determine whether serial biomarker measurements provide clinically useful information beyond standard wound and vascular assessments.

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Disclosure of conflict of interest

None.

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