Original Article

The Vascular Endothelial Growth Factor, Microalbuminuria, and β2-Microglobulin as Angiogenic and Renal Dysfunction Indicators in Patients with Diabetic Foot Ulcer

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ABSTRACT

Objective: To evaluate the serum vascular endothelial growth factor, microalbuminuria, and beta-2 microglobulin as concurrent markers of angiogenic impairment and renal injury.

Study Design: A cross-sectional study.

Place and Duration of Study: This study was conducted at the University of Babylon, Iraq from 1st November 2025 to 31st March 2026.

Methods: Ninety participants, 50 patients with confirmed diabetic foot ulcer, 20 diabetics without identifiable complications (positive control), and 20 healthy volunteers (negative control) were enrolled.

Results: Fasting blood sugar, glycated hemoglobin, vascular endothelial growth factor, microalbuminuria, and beta-2 microglobulin were significantly elevated in diabetic foot ulcer patients relative to both control groups ($P \leq 0.01$). A meaningful positive correlation was identified between serum vascular endothelial growth factor and microalbuminuria ($r=0.284$, $P=0.045$), pointing to a shared microvascular pathological process.

Conclusion: The routine and combined measurement of serum vascular endothelial growth factor, microalbuminuria, and beta-2 microglobulin is recommended as part of standard clinical monitoring for diabetic foot ulcer patients, providing clinicians the opportunity to intervene before complications become irreversible.

Key Words: Diabetic foot ulcer, Vascular endothelial growth factor, Beta 2-microglobulin, Microalbuminuria, Diabetic nephropathy, Angiogenesis

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INTRODUCTION

Diabetes mellitus (DM) continues its global expansion, placing mounting pressure on health systems at every income level.[1] When blood glucose remains poorly controlled over years, a cascade of tissue-damaging events unfolds - touching the heart, kidneys, eyes, and peripheral nerves alike.[2] For populations in lower-income settings, where screening and treatment remain out of reach for many, the resulting morbidity and economic loss are especially severe.[3]

Among the complications that clinicians dread most is the diabetic foot ulcer (DFU). It is the leading cause of non-traumatic lower limb amputation worldwide, and once established, it tends to recur – demanding prolonged wound care and repeated hospitalizations.[4] DFUs do not arise from a single cause; rather, they reflect the convergence of peripheral neuropathy, compromised vasculature, and defective immune defense, all driven by the chronic metabolic disturbance of diabetes.

Angiogenesis occupies a central position in DFU pathogenesis. Vascular endothelial growth factor (VEGF) is the principal mediator of new blood vessel formation, regulating endothelial cell migration and proliferation. In diabetic foot tissue, sustained hyperglycemia renders endothelial cells dysfunctional and markedly reduces local VEGF output, leaving wounds without the neovascularization needed for healing. A key molecular explanation lies in the disruption of the HIF-1/VEGF signaling axis: chronic high glucose blunts the hypoxic induction of pro-angiogenic factors, leaving the wound microenvironment in circulatory inadequacy.[5] Therapeutically, exogenous VEGF administration accelerates wound closure in DFU patients[6], while VEGF-A specifically drives early re-vascularization and re-epithelialization at wound margins.[7]

Diabetic foot ulcer rarely exists without concurrent renal involvement. Both conditions share a common root in chronic hyperglycemia-induced microvascular

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injury, which affects glomerular capillaries much as it affects peripheral vessels. Microalbuminuria - the earliest detectable sign of glomerular damage - is recognized as an independent cardiovascular risk indicator in diabetes and has been widely reported among Iraqi T2DM patients. A troubling limitation, however, is that kidney structure can deteriorate silently before albumin spills into the urine; roughly one-third of patients already show declining renal function before microalbuminuria becomes measurable, motivating the search for earlier complementary markers.[8]

Beta 2-microglobulin (β2-MG) fills part of this gap. This small protein associated with MHC class I antigens, passes freely through the glomerular filter and is reabsorbed almost entirely in the proximal tubule under normal conditions. When filtration slows or tubular cells are injured, serum β2-MG rises and crucially, this rise can precede detectable microalbuminuria, offering a window for earlier intervention in diabetic kidney disease.[9] The serum β2-MG as a stronger predictor of kidney failure requiring replacement therapy than conventional markers such as creatinine.[10] Measuring VEGF, microalbuminuria, and β2-MG together in DFU patients therefore captures the dual vascular-renal burden of this complication and may yield clinically actionable information before structural damage becomes irreversible.

METHODS

This cross-sectional study was conducted at University of Babylon, Iraq from 1st November 2025 to 31st March 2026 vide letter No. 11488/QM/Approval/JSDJNEHU dated October 28, 2025. Ninety participants were recruited and assigned to one of three groups: (1) 50 individuals with confirmed type 2 DM who had an active diabetic foot ulcer at enrollment, (2) 20 diabetic patients without identifiable complications (positive control), and (3) 20 apparently healthy individuals serving as negative controls. For every participant, demographic and clinical data including age, sex, and duration of diabetes were recorded in a standardized manner.[11]

Peripheral venous blood was drawn under aseptic conditions after a 12-hour fast, then centrifuged at 3000 rpm for 10 minutes; serum was stored at −80°C until analysis.[12] Fasting blood glucose was measured by the glucose oxidase method and HbA1c by high-performance liquid chromatography. Serum concentrations of microalbuminuria, β2-MG, and VEGF were quantified using commercially available ELISA kits per manufacturer specifications.[13]

All computations were performed using SPSS-26.0. One-way ANOVA compared group means, followed by pairwise testing via the LSD post hoc procedure. Pearson's correlation coefficient and simple linear regression examined relationships between continuous variables.[14] Statistical significance was defined as $P<0.05$.

RESULTS

There was significant ($P<0.05$) differences between age, depth of ulcer, side of ulcer and recurrence rate and no significant ($P>0.05$) differences between age and duration of diabetes (Table 1).

Table No. 1: Distribution of sample study according to gender, age, diabetic duration, depth of ulcer, side of ulcer and recurrence rate in patients group

Factor/Variables		No. n=50	%	P-value
Gender	Male	26	52.0	0.7773 NS
	Female	24	48.0	
Age (year)	< 50	10	20.0	0.0149*
	50 - 60	26	52.0	
	> 60	14	28.0	
Diabetic duration (years)	< 5	10	20.0	0.1323 NS
	5 – 10	20	40.0	
	> 10	20	40.0	
Depth of ulcer	Superficial	31	62.0	0.000**
	Deep	14	28.0	
	Deep with bone	5	10.0	
Side of ulcer	One foot	43	86.0	0.0001**
	Both feet	7	14.0	
Recurrence rate	Once	31	62.0	0.0001**
	Twice	6	12.0	
	2 - 3 times	11	22.0	
	> 3 times	2	4.0	

*P≤0.05 **P≤0.01, NS = Non-Significant

Table 2: Comparison between groups in FBS, HbA1c, Microalbuminuria, B2 Microglobulin and VEGF

Parameters	Patients with DFU	Patients without DFU	Negative control	L.S.D.	P-value
FBS (mg/dl)	247.02±5.23 a	194.20±10.77 b	108.60±1.16 c	48.219**	0.0001
HbA1c (%)	8.57±0.26 a	7.84±0.19 a	5.09±0.07 b	0.7794**	0.0001
Microalbuminuria (mg/L)	71.83±9.95 a	45.17±2.92 b	10.83±0.80 c	27.974**	0.0002
B2 Microglobulin (mg/L)	16.83±0.28 a	8.46±1.72 b	5.50±0.81 c	2.397**	0.0001
VEGF (Pg/ml)	320.56 ±10.97 a	246.92 ±9.24 b	154.61 ±6.98 c	35.116**	0.0001

Means with different letters in the same column differ significantly. **P≤0.01

There was significant (P<0.05) differences in FBS, HbAIc, microalbuminuria, B2 microglobulin and VEGF between patients with diabetic foot and patients without diabetic foot (Table 2).

There was correlation between vascular endothelial growth factor, fasting blood sugar, glycated hemoglobin, Microalbuminuria and beta 2 Microglobulin in patients group (Table 3, Figs.1-2).

Table 3: Correlation between VEGF, FBS, HbA1c, Microalbuminuria and B2 Microglobulin in patients group

Parameters	FBS	HbA1c	Microalbuminuria	B2 MG	VEGF
FBS	—	p=0.0001** r=0.574	p=0.808 NS r=0.035	p=0.756 NS r=-0.045	p=0.212 NS r=-0.179
HbA1c	—	—	p=0.882 NS r=0.022	p=0.492 NS r=0.100	p=0.529 NS r=-0.091
Microalbuminuria	—	—	—	p=0.216 NS r=0.178	p=0.046* r=0.284
B2 Microglobulin	—	—	—	—	p=0.598 NS r=0.076
VEGF	—	—	—	—	—

*P≤0.05, **P≤0.01, NS: Non-significant

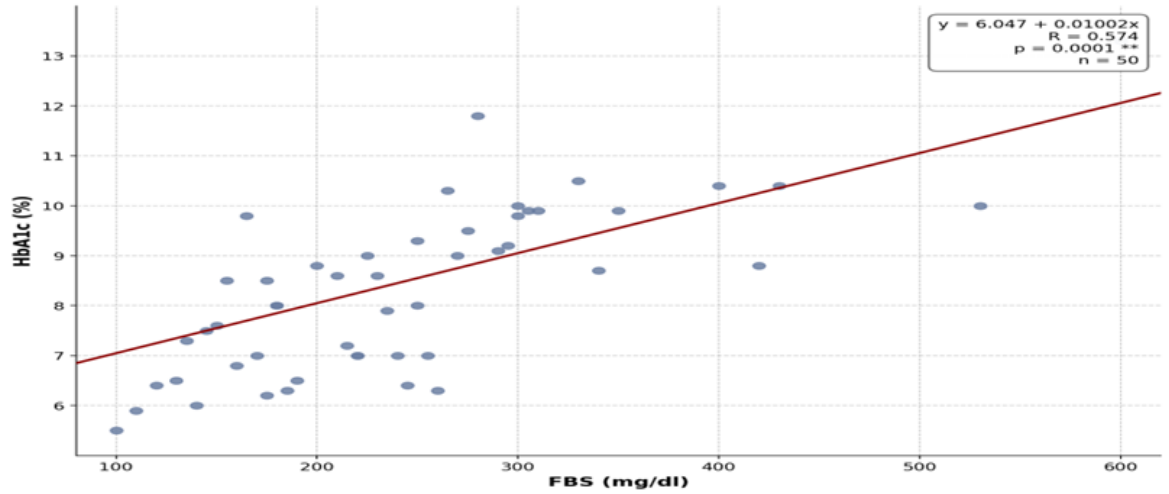

Figure No. 1: Positive linear regression between FBS (mg/dl) and HbA1c (%) in diabetic foot ulcer patients

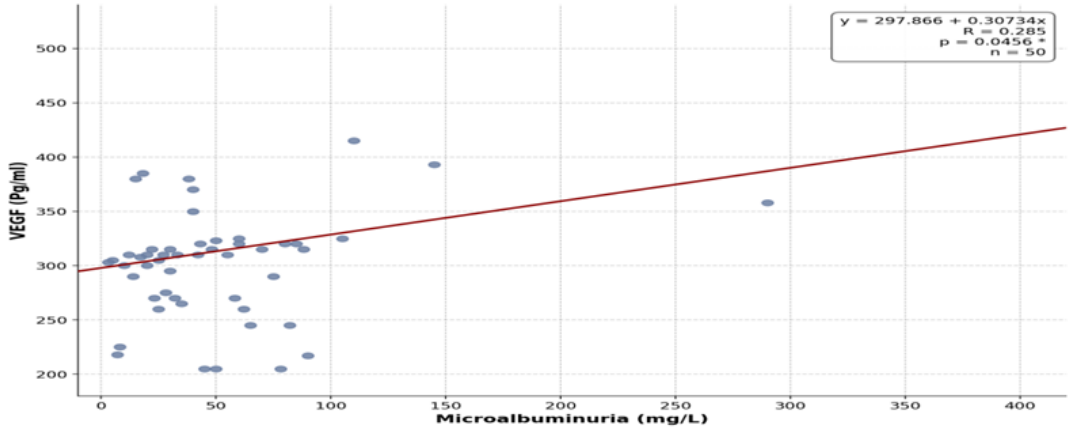

Figure No. 2: Weak positive linear regression between VEGF (pg/ml) and microalbuminuria (mg/L) in diabetic foot ulcer patients

DISCUSSION

The glycemic picture that emerged was unambiguous. FBS averaged 247.02±15.23 mg/dl in DFU patients - well above the 194.20±10.77 mg/dl in uncomplicated diabetics and far beyond the 108.60 ± 1.16 mg/dl in healthy controls (P=0.0001). HbA1c followed the same hierarchy: 8.57±0.26%, 7.84±0.19%, and 5.09±0.07%,

respectively (P=0.0001). HbA1c values were statistically comparable between the two diabetic groups, suggesting that chronic glycemic burden is a shared feature across T2DM rather than exclusive to those with ulcers. What the DFU group does exhibit is a compounding effect: poor long-term control simultaneously intensifies local ischemia and suppresses immune responses, creating conditions that actively prevent tissue repair.[4]

At the molecular level, persistent hyperglycemia restrains HIF-1 transcriptional activity, which in turn dampens VEGF expression in wound tissue and locks the local vasculature in a state of inadequacy.[5] Population data reinforce what the bench science predicts: HbA1c values above 8% are independently linked to both microvascular and macrovascular complications, including peripheral neuropathy and foot ulceration[1], and are directly associated with reduced wound-tissue VEGF output and poorer DFU prognosis.[15] A pooled analysis spanning more than 141 million participants from 1108 studies confirmed that chronic fasting hyperglycemia and elevated HbA1c consistently drive organ damage across diverse populations worldwide.[2]

Microalbuminuria rose in a clear stepwise pattern - from 10.83±0.80 mg/L in healthy controls, to 45.17±2.92 mg/L in uncomplicated diabetics, and peaking at 71.83±9.95 mg/L in DFU patients (P=0.0002). This gradient is not coincidental. Glomerular capillaries, like peripheral vessels, are vulnerable to the hemodynamic and oxidative stress of sustained hyperglycemia; as that damage accumulates, albumin leaks through the filtration barrier in progressively greater amounts. The finding therefore tracks a deepening of renal microvascular injury that parallels the overall severity of diabetic complications.

As the earliest detectable marker of diabetic nephropathy and an independent cardiovascular risk predictor[8], microalbuminuria holds a well-established clinical role - yet its limitations deserve acknowledgment. Around one-third of patients experience declining renal function before any albumin becomes detectable in the urine, meaning reliance on this marker alone will miss a meaningful share of early cases.[8] In the context of DFU, chronic hyperglycemia and microvascular disease are the shared soil from which both the ulcer and nephropathy grow, and microalbuminuria has been validated as a useful surrogate for the total vascular burden these patients carry.[4] Without treatment, up to 80-85% of insulin-dependent patients who develop microalbuminuria progress to advanced nephropathy within roughly a decade[13], and rising global microalbuminuria rates track closely with the spread of diabetic nephropathy in regions of poor glycemic control.[3]

The β2-MG findings were striking. DFU patients showed serum levels of 16.83±0.28 mg/L more than double the 8.46±1.72 mg/L in uncomplicated diabetics and nearly three times the 5.50±0.81 mg/L in healthy controls (P=0.0001). This sharp, complication-severity-dependent elevation points directly to progressive disruption of both glomerular filtration and proximal tubular re-absorption. Because β2-MG is ordinarily cleared with high efficiency at the tubule, rising serum concentrations sensitively reflect injury at that segment before conventional renal markers shift.

This early-detection advantage is increasingly recognized. Tubular damage in diabetic nephropathy frequently precedes glomerular deterioration, and β2-MG's sensitivity to proximal tubule dysfunction makes it a more timely indicator than albumin-based tests for some patients.[9] Serum β2-MG has also been shown to outperform standard markers including creatinine and albumin in predicting end-stage kidney disease requiring replacement therapy in biopsy-confirmed diabetic nephropathy.[10] A large prospective cohort study further established β2-MG as an independent predictor of ESRD and all-cause mortality in high-risk diabetic populations.[16] The markedly higher β2-MG concentrations in DFU patients compared to uncomplicated diabetics suggest that active ulceration is associated with accelerated renal tubular decline and reinforce the case for including this biomarker in routine DFU follow-up.[17]

Mean serum VEGF followed a consistent upward trajectory: 154.61±6.98 pg/ml in healthy controls, 246.92±9.24 pg/ml in uncomplicated diabetics, and 320.56±10.97 pg/ml in DFU patients (P=0.0001). At first glance, the highest VEGF in the sickest group might seem paradoxical if VEGF drives angiogenesis, why are DFU wounds failing to heal? The answer lies in the distinction between systemic compensatory upregulation and local functional impairment. Circulating VEGF rises as the body attempts to counteract peripheral ischemia, but the endothelial machinery in a chronically hyperglycemic environment is too damaged to respond effectively.[18]

Locally, endothelial dysfunction under persistent high glucose substantially reduces VEGF synthesis within wound tissue, leaving neovascularization deficient precisely where it is needed (Huang et al., 2025). The HIF-1/VEGF pathway—normally activated by tissue hypoxia cannot mount an adequate response when hyperglycemia disrupts HIF-1α activity, reducing downstream pro-angiogenic signaling and worsening local oxygen deprivation.[5] Compounding this, activation of the polyol, protein kinase C, hexosamine, and AGE pathways generates reactive oxygen species, promotes chronic inflammation, and further suppresses HIF-1α, collectively stalling angiogenesis and tissue repair.[19] Elevated AGEs together with TNF-α also stimulate secretion of soluble VEGFR-1, which sequesters free VEGF as a decoy receptor, stripping it of biological activity at the wound site.[20]

Despite these barriers, therapeutic strategies targeting VEGF retain real promise. Exogenous VEGF delivery promotes wound closure through vasodilation, basement membrane proteolysis, and coordinated endothelial migration and proliferation.[6] VEGF-A appears especially important in initiating the earliest angiogenic steps and epithelial re-growth at wound margins, while VEGF-C contributes a complementary role by promoting lymphangiogenesis during granulation tissue formation.[15] Altogether, the VEGF profile in this cohort underscores why restoring its local bioactivity remains a priority research target for improving DFU outcomes.[4]

CONCLUSION

Patients with diabetic foot ulcers demonstrated significantly elevated serum concentrations of serum vascular endothelial growth factor, microalbuminuria, and beta-2 microglobulin compared to both diabetic and healthy control groups - evidence of concurrent angiogenic dysregulation and progressive renal impairment occurring side by side. The significant positive correlation between serum vascular endothelial growth factor and microalbuminuria suggests these two processes share an underlying microvascular mechanism rather than developing independently. Combined with glycemic indices, this biomarker triad offers a broader and more clinically meaningful evaluation of the systemic impact of diabetes. The routine and combined measurement of serum vascular endothelial growth factor, microalbuminuria, and beta-2 microglobulin is recommended as part of standard clinical monitoring for diabetic foot ulcer patients, providing clinicians the opportunity to intervene before complications become irreversible.

Author's Contribution:

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Drafting or Revising Critically:	Hind Chassab Karam, Walaa Salih Hassan
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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