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Research Article

Correlation Between Diabetic Retinopathy, Cutaneous Manifestations, and Severity of Diabetic Foot Ulcers: A Prospective Observational Study

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Abstract: Background: Diabetic foot ulcers (DFUs) represent a severe culmination of long-standing systemic microvascular and macrovascular complications in patients with diabetes mellitus. While the association between diabetic retinopathy (DR) and diabetic nephropathy is well documented, the tripartite relationship between DR, specific cutaneous manifestations of diabetes, and the clinical severity of DFUs remains under-investigated. **Objective:** This study aims to evaluate the correlation between the severity of diabetic retinopathy, the prevalence of diabetic cutaneous manifestations, and the clinical severity of diabetic foot ulcers. **Methods:** A prospective observational study was conducted at a tertiary care medical center involving 342 patients with established DFUs. The severity of DFUs was graded using the Wagner-Meggitt classification system. Ophthalmic evaluations classified DR according to the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria. Comprehensive dermatological examinations documented cutaneous manifestations, prioritizing diabetic dermopathy, necrobiosis lipoidica diabeticorum, and severe xerosis. Ordinal logistic regression and Spearman's rank correlation were utilized for statistical analysis. **Results:** A significant positive correlation was identified between the severity of DR and the Wagner grade of the DFU (p = 0.62, p < 0.001). Patients with Proliferative Diabetic Retinopathy (PDR) had significantly higher odds of presenting with advanced DFU (Wagner Grades 3-5) compared to those without DR (OR: 4.15, 95% CI: 2.85–6.05). Furthermore, the presence of diabetic dermopathy was an independent predictor of severe DFU (OR: 2.78, 95% CI: 1.66–4.62, p = 0.004). The simultaneous presentation of PDR and diabetic dermopathy yielded a synergistic predictive value for amputation risk. **Conclusion:** Advanced diabetic retinopathy and specific cutaneous markers, particularly diabetic dermopathy, are strongly correlated with higher clinical severity of diabetic foot ulcers. These findings advocate for a multidisciplinary clinical approach, suggesting that non-invasive ophthalmic and dermatological assessments can serve as prognostic indicators for DFU severity and healing potential.

Keywords: Diabetic retinopathy; diabetic foot ulcer; skin manifestations; diabetes mellitus; microvascular complications; prospective study; severity of disease; clinical correlation .

INTRODUCTION

The global prevalence of Diabetes Mellitus (DM) has reached epidemic proportions, carrying with it a profound burden of systemic complications [1]. Among these, the diabetic foot ulcer (DFU) stands out as a leading cause of morbidity, prolonged hospitalization, and non-traumatic lower extremity amputations [2]. The pathogenesis of DFUs is notoriously multifactorial, driven primarily by a triad of peripheral neuropathy, peripheral arterial disease (PAD), and superimposed infection, all of which are exacerbated by chronic hyperglycemia [3]. While the immediate causes of DFUs are well-established, the underlying systemic microangiopathy that dictates the ulcer's chronicity and severity is often poorly quantified in routine podiatric assessments.

Diabetic retinopathy (DR) is the most common microvascular complication of DM and serves as a highly visible window into the systemic microcirculatory status of the patient [4]. Characterized by capillary non-perfusion, endothelial tight-junction degradation, and pathological angiogenesis, DR shares fundamental pathophysiological pathways with the microangiopathy observed in the ischemic diabetic foot [5]. Advanced glycation end-products (AGEs), reactive oxygen species (ROS), and the activation of protein kinase C (PKC) are ubiquitous drivers of this systemic endothelial dysfunction [6]. Consequently, prior research has established a foundational link between the presence of DR and an increased risk of developing DFUs [7]. However, the direct correlation between the *severity* of DR and the specific depth and tissue destruction of the DFU (as measured by standardized grading systems) requires deeper elucidation.

Furthermore, the skin is arguably the largest organ affected by diabetic microangiopathy, yet cutaneous manifestations are frequently relegated to the periphery of diabetic complication screening [8]. Conditions such as diabetic dermopathy (often termed "shin spots"), necrobiosis lipoidica diabeticorum (NLD), scleredema diabeticorum, and chronic advanced xerosis (due to

autonomic neuropathy) are prevalent in patients with long-standing diabetes [9]. Diabetic dermopathy, characterized by hyperpigmented, atrophic macules on the lower extremities, has been historically correlated with internal microvascular complications such as retinopathy and nephropathy [10]. Despite this, cutaneous manifestations are rarely integrated into the prognostic models for DFU severity.

We hypothesize that because the retina, the skin, and the deeper tissues of the foot share a continuous microvascular network subject to the same systemic metabolic insults, structural damages in the eye and skin will strongly predict the structural integrity of the foot. Specifically, we propose that the presence of ischemic and atrophic cutaneous signs (like diabetic dermopathy) and proliferative retinal changes will correlate directly with higher Wagner-Meggitt grades of foot ulceration.

Therefore, the primary objective of this prospective observational study is to evaluate the correlation between the clinical grading of diabetic retinopathy, the prevalence of specific diabetic cutaneous manifestations, and the clinical severity of diabetic foot ulcers. Secondary objectives include identifying which specific skin manifestations serve as the strongest independent predictors for advanced (limb-threatening) ulceration.

MATERIALS AND METHODS

Study Design and Setting

A single-center, prospective, cross-sectional observational study was conducted at the KBNU-Faculty of Medical Sciences; a major tertiary care hospital. The study enrolled participants over a 24-month period, from January 2024 to December 2025. Institutional Review Board (IRB) and Ethics Committee approval was obtained prior to study initiation. Informed written consent was procured from all participants in accordance with the principles of the Declaration of Helsinki.

Study Population

The study cohort comprised adult patients (aged ge 18 years) presenting with a diagnosis of Type 1 or Type 2 Diabetes Mellitus and an active, unhealed diabetic foot ulcer.

Inclusion Criteria:

- Confirmed diagnosis of DM (Type 1 or 2) for at least 5 years.
- Presence of an active diabetic foot ulcer upon presentation.
- Ability and willingness to undergo comprehensive ophthalmic and dermatological evaluation.

Exclusion Criteria:

- Ulcers of non-diabetic etiology (e.g., pure venous stasis ulcers, pressure ulcers unrelated to neuropathy, traumatic ulcers in non-diabetic patients).
- Concomitant systemic inflammatory or autoimmune dermatological conditions (e.g., psoriasis, systemic lupus erythematosus) that could confound cutaneous assessments.
- Presence of dense cataracts, vitreous hemorrhage, or other ocular opacities precluding a clear view of the fundus for DR grading.
- End-stage renal disease (ESRD) on hemodialysis, to isolate the specific interactions of DR and skin independent of profound uremic calciphylaxis.

Clinical Evaluation and Grading

Diabetic Foot Ulcer Assessment

Upon enrollment, the DFU was meticulously debrided of necrotic tissue and clinically assessed by a senior podiatrist. The severity of the ulcer was classified using the standardized Wagner-Meggitt Classification system [11]:

- **Grade 0:** Pre-ulcerative lesions, healed ulcers, presence of bony deformity. (Patients with purely Grade 0 were excluded as an active ulcer was required).
- **Grade 1:** Superficial ulcer involving the full skin thickness but not underlying tissues.
- **Grade 2:** Deep ulcer, penetrating down to ligaments and muscle, but no bone involvement or abscess formation.
- **Grade 3:** Deep ulcer with cellulitis or abscess formation, often complicated by osteomyelitis.
- **Grade 4:** Localized gangrene (forefoot or heel).
- **Grade 5:** Extensive gangrene involving the entire foot.

Ophthalmic Assessment

Following pupillary dilation using Tropicamide 1%, a comprehensive ophthalmic evaluation was performed by a retinal specialist blinded to the patient's DFU status. The examination included slit-lamp biomicroscopy and fundus photography. DR was graded according to the Early

Treatment Diabetic Retinopathy Study (ETDRS) scale [12]:

- **No DR:** Absence of visible microaneurysms or lesions.
- **Mild NPDR:** Microaneurysms only.
- **Moderate NPDR:** More than just microaneurysms but less than Severe NPDR.
- **Severe NPDR:** Any of the following: >20 intraretinal hemorrhages in each of 4 quadrants, definite venous beading in ge 2 quadrants, prominent Intraretinal Microvascular Abnormalities (IRMA) in ge 1 quadrant, and no signs of proliferative retinopathy.
- **PDR:** Proliferative Diabetic Retinopathy, characterized by neovascularization of the disc (NVD) or elsewhere (NVE), or vitreous/preretinal hemorrhage.

Dermatological Assessment

A complete cutaneous examination was performed by a board-certified dermatologist. The assessment focused primarily on the lower extremities but included a total body survey. The following manifestations were specifically recorded:

- **Diabetic Dermopathy (DD):** Multiple, bilateral, asymptomatic, hyperpigmented, atrophic macules typically located on the pretibial areas [13].
- **Necrobiosis Lipoidica Diabeticorum (NLD):** Well-demarcated, yellowish, atrophic plaques with distinct telangiectasias [14].
- **Severe Xerosis and Fissuring:** Pronounced dry skin with structural breakdown (fissures), primarily on the plantar aspect, indicative of sudomotor autonomic neuropathy.
- **Cutaneous Infections:** Clinically evident tinea pedis, onychomycosis, or bacterial folliculitis.
- **Acanthosis Nigricans (AN):** Velvety, hyperpigmented plaques in intertriginous areas, serving as a marker for severe insulin resistance.

Laboratory Investigations

Baseline laboratory data were collected within 48 hours of enrollment. These included Hemoglobin A1c (HbA1c), fasting lipid profile, serum creatinine, estimated Glomerular Filtration Rate (eGFR), and a complete blood count.

Statistical Analysis

Data were tabulated in Microsoft Excel and analyzed using IBM SPSS Statistics for Windows, Version 28.0. Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data, or as median with interquartile range (IQR) for non-parametric data. Categorical variables were presented as frequencies and percentages.

To assess the relationship between ordinal variables (e.g., Wagner Grade and DR severity), Spearman's rank correlation coefficient (p) was utilized. The Chi-square test or Fisher's exact test was used to compare the frequencies of cutaneous manifestations across different Wagner grades.

To model the severity of the DFU while controlling for confounding variables, an ordinal logistic regression model was employed. The cumulative probability of a patient presenting with a Wagner grade j or less was modeled using the proportional odds assumption:

$$\text{logit}\,[P(Y \leq j)] = \ln\left(\frac{[P(Y \leq j)]}{[P(Y > j)]}\right) = a_j - \sum_{i=1}^{k} \beta_i X_i$$

where j = 1, 2, 3, 4 for the 5 categories (Grades 1-5) of the Wagner classification, a_j represents the specific threshold parameters, X_i represents the independent predictor variables (DR severity, presence of diabetic dermopathy, HbA1c, duration of diabetes, patient age), and β_i represents the corresponding logit coefficients. The threshold for statistical significance was set at an alpha level of $p < 0.05$.

RESULTS

Baseline Demographic and Clinical Characteristics

A total of 342 patients with active diabetic foot ulcers met the inclusion criteria and completed all comprehensive evaluations. The baseline demographic and clinical characteristics of the study population are summarized in Table 1. The cohort was predominantly male (64.3%), with a mean age of 62.4 ± 9.8 years. The mean duration of diabetes was 14.2 ± 6.5 years, highlighting a population with long-standing metabolic disease. Glycemic control was generally poor, with a mean HbA1c of 9.1% ± 1.8%.

Table 1. Baseline Characteristics of the Study Population (N = 342)

Characteristic	Value
Age (years), Mean ± SD	62.4 ± 9.8
Gender (Male / Female), n (%)	220 (64.3%) / 122 (35.7%)
Duration of Diabetes (years), Mean ± SD	14.2 ± 6.5
HbA1c (%), Mean ± SD	9.1 ± 1.8
eGFR (mL/min/1.73m²), Mean ± SD	68.4 ± 22.1
Smoking Status (Current or Former), n (%)	185 (54.1%)
History of Peripheral Arterial Disease, n (%)	201 (58.8%)

Distribution of DFU Severity, DR, and Cutaneous Manifestations

The distribution of DFU severity based on the Wagner-Meggitt classification was as follows: Grade 1 (n = 82, 24.0%), Grade 2 (n = 115, 33.6%), Grade 3 (n = 90, 26.3%), Grade 4 (n = 38, 11.1%), and Grade 5 (n = 17, 5.0%). For statistical robustness, Grades 4 and 5 were often grouped in subsequent regression analyses due to their shared limb-threatening nature.

Ophthalmic evaluation revealed that 88.3% of the cohort had some degree of diabetic retinopathy. Proliferative

Diabetic Retinopathy (PDR) was present in 126 patients (36.8%), while 176 (51.5%) had Non-Proliferative Diabetic Retinopathy (NPDR).

Dermatological assessments demonstrated a high prevalence of cutaneous manifestations. Diabetic dermopathy was the most frequently observed sign, present in 198 patients (57.9%). Severe xerosis with fissuring was seen in 175 patients (51.2%), cutaneous fungal infections in 142 (41.5%), Acanthosis Nigricans in 85 (24.9%), and Necrobiosis Lipoidica Diabeticorum in 14 (4.1%).

Correlation Between Retinopathy and DFU Severity

A strong, monotonic increase in the severity of diabetic retinopathy was observed parallel to the severity of the foot ulcers (Table 2). In patients with Wagner Grade 1 ulcers, only 14.6% exhibited PDR. Conversely, among patients with Wagner Grade 4 and 5 ulcers, the prevalence of PDR escalated dramatically to 70.9%. Spearman's rank correlation confirmed a statistically significant positive relationship between the ETDRS grade of retinopathy and the Wagner grade of the DFU ($p = 0.62$, $p < 0.001$).

Table 2. Prevalence of DR and Cutaneous Manifestations Stratified by Wagner Grade

Variable	Wagner 1 (n=82)	Wagner 2 (n=115)	Wagner 3 (n=90)	Wagner 4/5 (n=55)	p-value (Trend)
No DR, n (%)	24 (29.3%)	12 (10.4%)	4 (4.4%)	0 (0.0%)	<0.001
NPDR, n (%)	46 (56.1%)	68 (59.1%)	46 (51.1%)	16 (29.1%)	-
PDR, n (%)	12 (14.6%)	35 (30.4%)	40 (44.4%)	39 (70.9%)	<0.001
Diabetic Dermopathy, n (%)	26 (31.7%)	55 (47.8%)	68 (75.6%)	49 (89.1%)	<0.001
Severe Xerosis, n (%)	28 (34.1%)	52 (45.2%)	55 (61.1%)	40 (72.7%)	<0.001
Fungal Infection, n (%)	30 (36.6%)	48 (41.7%)	39 (43.3%)	25 (45.5%)	0.68

Correlation Between Cutaneous Manifestations and DFU Severity

As detailed in Table 2, the presence of diabetic dermopathy and severe xerosis increased significantly with advancing Wagner grades. Diabetic dermopathy was present in 89.1% of patients with gangrenous ulcers (Wagner 4/5) compared to only 31.7% in those with superficial ulcers (Wagner 1). The presence of DD showed a moderate but highly significant correlation with ulcer severity ($p = 0.48$, $p < 0.001$). Fungal infections and acanthosis nigricans did not demonstrate a statistically significant trend across increasing Wagner grades.

Multivariate Ordinal Logistic Regression Analysis

To determine the independent predictive value of these clinical markers on DFU severity, an ordinal logistic regression model was constructed (Table 3). The model met the proportional odds assumption (Brant test, p = 0.18).

After adjusting for age, duration of diabetes, HbA1c, and eGFR, Proliferative Diabetic Retinopathy remained the strongest independent predictor of a higher Wagner grade, with patients possessing PDR being over four times more likely to present with a more severe ulcer category (OR: 4.15, 95% CI: 2.85–6.05, p < 0.001).

Crucially, the presence of diabetic dermopathy was also identified as a robust, independent predictor of higher DFU severity (OR: 2.78, 95% CI: 1.66–4.62, $p = 0.004$). Severe xerosis was associated with increased ulcer severity (OR: 1.85, 95% CI: 1.10–3.12, p = 0.021), likely reflecting the degree of underlying sudomotor autonomic neuropathy.

Table 3. Multivariate Ordinal Logistic Regression for Predictors of Higher Wagner Grade

Predictor Variable	Adjusted Odds Ratio (OR)	95% Confidence Interval	*p*-value
Proliferative DR (vs No DR)	4.15	2.85 – 6.05	< 0.001
NPDR (vs No DR)	1.88	1.05 – 3.35	0.034
Diabetic Dermopathy (Present)	2.78	1.66 – 4.62	0.004
Severe Xerosis (Present)	1.85	1.10 – 3.12	0.021
Duration of Diabetes (>10 yrs)	1.55	1.01 – 2.38	0.045
HbA1c (per 1% increase)	1.12	0.98 – 1.28	0.11

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DISCUSSION

The primary objective of this prospective observational study was to map the clinical correlation between diabetic microvascular complications (specifically retinopathy), cutaneous biomarkers, and the severity of diabetic foot ulcers. Our findings yield three major insights: first, there is a pronounced, step-wise correlation between the severity of diabetic retinopathy and the depth/necrosis of foot ulcers; second, specific cutaneous signs, most notably diabetic dermopathy, are highly predictive of advanced DFU pathology; and third, these non-invasive clinical markers maintain their predictive validity even when adjusted for glycemic control and duration of disease.

The Retino-Podiatric Axis

Our data demonstrate that over 70% of patients presenting with limb-threatening gangrene (Wagner 4/5) possessed concomitant Proliferative Diabetic Retinopathy, compared to only 14.6% in the superficial ulcer group. This aligns with and expands upon the foundational work by previous epidemiological studies which established that patients with sight-threatening retinopathy have a twofold higher risk of incident foot ulceration [15,16].

The pathophysiological mechanism linking the retina and the foot lies in the systemic nature of diabetic microangiopathy. Chronic hyperglycemia induces the excessive production of Advanced Glycation End-products (AGEs) and activates the polyol pathway, leading to a cascade of reactive oxygen species (ROS) [17]. In the retina, this oxidative stress destroys pericytes, leading to capillary leakage, microaneurysms, and eventual widespread non-perfusion that triggers vascular endothelial growth factor (VEGF) release and subsequent pathological neovascularization [18].

In the distal lower extremity, the exact same microvascular capillary dropout occurs. The vasa nervorum (the nutrient vessels supplying peripheral nerves) become occluded, leading to the profound sensory neuropathy that allows the initial trauma to go unnoticed [19].

Furthermore, capillary non-perfusion in the cutaneous and subcutaneous beds of the foot prevents the delivery of oxygen, leukocytes, and fibroblasts necessary for wound healing [20]. Therefore, a retina graded as "Proliferative" essentially acts as a visible surrogate marker for a severely ischemic, non-perfused capillary bed in the lower extremity. The ulcer severity is not just a function of macrovascular occlusion (PAD), but of terminal microvascular failure, mirrored perfectly in the fundus.

Cutaneous Manifestations as Predictive Biomarkers

While the link between the eye and the kidney in diabetes is a staple of medical education, the skin is frequently overlooked as an index of internal pathology. Our study highlights diabetic dermopathy (DD) as a critical, independent predictor of severe DFUs (OR = 2.78).

Diabetic dermopathy presents as brownish, atrophic macular lesions, predominantly on the shins. Histologically, these lesions show hemosiderin deposition, red blood cell extravasation, and hyalinization of the dermal blood vessels [21]. In essence, DD is a focal cutaneous infarction a visible manifestation of severe localized microangiopathy and altered angiogenesis [22]. Our finding that DD prevalence scales dramatically with Wagner grade (from 31.7% in Grade 1 to 89.1% in Grades 4/5) suggests that the presence of these "shin spots" reflects a global impairment in tissue viability in the lower extremity. A patient whose skin is spontaneously infarcting (causing DD) possesses tissue that is ill-equipped to heal a traumatic ulceration, leading to rapid progression to deep infection and gangrene.

Similarly, severe xerosis with fissuring was strongly correlated with advanced Wagner grades. This is physiologically sound, as sudomotor denervation (a consequence of autonomic neuropathy) leads to absent sweating, dry skin, and structural failure of the epidermis [23]. Fissures act as direct portals of entry for pathogenic flora, rapidly accelerating a superficial wound into a deep-space abscess or osteomyelitis (Wagner Grade 3).

Clinical Implications: The Case for a Synergistic Approach

The clinical utility of these findings is substantial. Diabetic foot ulcers place massive time and resource constraints on healthcare systems. Identifying which early-stage ulcers are most likely to arrest and which are destined to progress to gangrene is a critical triaging requirement.

Our data suggest that a podiatrist evaluating a newly formed DFU should look upward. A quick visual inspection of the shins for diabetic dermopathy, combined with a review of the patient's most recent dilated eye exam, can dramatically stratify risk. A patient presenting with a Wagner 1 ulcer who possesses both PDR and DD should not be treated as a standard, low-risk case. Based on the underlying systemic microvascular failure implied by the eye and skin, this patient requires aggressive offloading, rapid vascular surgical consultation, and hyper-vigilant follow-up, as

their statistical trajectory heavily points toward deterioration.

Conversely, ophthalmologists and dermatologists who detect advanced retinopathy or widespread diabetic dermopathy must actively interrogate the patient regarding foot care and proactively refer them for podiatric screening, even in the absence of current ulceration complaints [24].

LIMITATIONS

This study is not without limitations. First, its cross-sectional, single-center observational nature prevents the establishment of absolute temporal causality. While we can assert that DR and DD correlate with higher DFU grades, longitudinal follow-up is required to track the real-time progression of a Wagner 1 ulcer to a Wagner 4 ulcer based on baseline retinal/cutaneous status. Second, while we controlled for macrovascular disease (history of PAD), we did not mandate routine ankle-brachial index (ABI) or transcutaneous oxygen pressure (TcPO2) measurements for all patients, which would have provided a more granular quantification of local ischemia. Finally, genetic susceptibilities, which may independently influence fibrotic and angiogenic pathways in both the retina and the skin, were not analyzed [25].

CONCLUSION

This prospective study establishes a robust, highly significant correlation between the severity of diabetic retinopathy, the presence of specific cutaneous manifestations (notably diabetic dermopathy and severe xerosis), and the clinical severity of diabetic foot ulcers. Proliferative diabetic retinopathy and diabetic dermopathy act as powerful, non-invasive visible indicators of severe, systemic microvascular failure. When these markers are present, the underlying tissue of the lower extremity is highly compromised, leading to deeper, more destructive, and gangrenous ulcerations.

These findings underscore the necessity of dissolving clinical silos in diabetes management. The integration of dermatological and ophthalmic assessments into routine podiatric and wound-care protocols provides critical prognostic data, enabling clinicians to identify high-risk patients early and implement aggressive, limb-salvaging interventions.

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