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Stepping Into Danger: Risk Factors for Diabetic Foot Infections in Pakistan

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ABSTRACT

OBJECTIVE: This study aimed to identify the patient-related risk factors for diabetic foot infections and assess their impact on disease progression.

METHODOLOGY: A Cross-sectional study was conducted at Dow University Hospital, Karachi, from June to December 2023. A total of 150 diabetic patients were included using a non-probability purposive sampling technique.

The inclusion criteria for this study consisted of diagnosed diabetic patients aged (57.11±9.83) years, with or without diabetic foot infections, who were willing to participate and provide consent. The exclusion criteria included non-diabetic individuals, patients with foot ulcers or infections unrelated to diabetes (e.g; trauma), those with incomplete clinical records or missing data, and individuals unwilling to participate. Data were collected using a self-designed questionnaire and clinical records, focusing on demographics, biochemical markers, and clinical factors such as peripheral neuropathy, peripheral arterial disease, osteomyelitis, and smoking history. Statistical analysis was performed using SPSS version 23.

RESULTS: The study revealed that peripheral neuropathy (OR = 3.2), peripheral arterial disease (OR = 3.1), and smoking (OR = 2.0) were significant independent risk factors for diabetic foot infections. Infected patients also exhibited poor glycemic control, as evidenced by elevated HbA1c levels and an abnormal lipid profile characterized by higher LDL-c and lower HDL-c levels compared to the uninfected group.

CONCLUSION: Peripheral neuropathy, Peripheral arterial disease, and smoking are major risk factors for diabetic foot infections.

KEYWORDS: Diabetes mellitus, Diabetic foot ulcer, peripheral neuropathy, peripheral arterial disease.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by elevated blood glucose levels [1]. There are two renowned types of DM, Type-1 (T1DM) and Type-2 (T2DM) [3]. T1DM is usually detected in adolescence or childhood, resulting from the immune system destroying the pancreatic beta cells responsible for insulin production[2]. By contrast, insulin resistance and decreased insulin production are the primary causes of type 2 diabetes mellitus (T2DM), which is more common[4]. Diabetes mellitus is more than a metabolic ailment and a significant risk for a wide range of consequences, especially cardiovascular conditions such as peripheral arterial disease (PAD), atherosclerotic heart disease, and stroke [5]. T2DM can lead to serious outcomes, including impairment of the kidneys (nephropathy), retinal damage (retinopathy), and nerve damage (neuropathy), all resulting from consistently elevated blood sugar levels [6].

In diabetic patients, dyslipidemia (abnormal cholesterol levels), insulin resistance, hyperglycemia (high blood sugar), and hypertension are among the factors that accelerate the development of micro and macro-vascular changes [7]

Diabetic foot infections are another substantial complication of T2DM and a significant challenge in diabetes treatment and often lead to severe complications and adverse outcomes [8]. 40–60 million people with diabetes around the world suffer from diabetic foot ulcers [9]. Recognizing the risk factors associated with this medical problem is crucial for effective prevention and timely resolution.

Long-term diabetes, old age, male gender, poor blood sugar regulation, and concomitant illnesses, including peripheral neuropathy (PN) or peripheral artery disease (PAD), weaken the body's immune system, delay wound healing, and reduce foot sensation, all of which increase the risk of infection.

Diabetic foot infections are highly influenced by foot-specific abnormalities, such as callus tissue formation, ulcerations, hammertoes, bunions, and Charcot's disease[11]. These abnormalities increase friction and pressure on the foot, leading to skin breakdown and ulcer development in patients with diabetes[12].

In individuals with diabetic foot, systemic factors such as immunodeficiency and decreased wound healing all increase the risk of infection[13]. Chronic hyperglycemia reduces the body's ability to fight infections as it affects immune cells being activated [14]. A common consequence of peripheral neuropathy is an impairment of protective sensation in the feet, making it harder for patients to detect wounds or injuries[15]. Furthermore, inadequate circulation and compromised microvascular perfusion limit gaseous exchange and the transport of nutrients across damaged tissues, delaying the healing process and increasing the risk of bacterial infection[16].

This study aimed to identify patient-related risk factors for diabetic foot infections and assess their impact on the progression and outcomes of these infections. This study highlights the role of biochemical markers (HbA1c, LDL-c, HDL-c) as additional risk factors for diabetic foot infections in Pakistani patients. Unlike previous research, it provides region-specific data to guide early detection and prevention in resource-limited settings. The findings emphasize the importance of metabolic control, alongside neuropathy and vascular complications, in reducing the risk of developing diabetic foot infection (DFI). This novel approach can help develop targeted public health strategies to prevent amputations.

METHODOLOGY

This cross-sectional study included 150 patients with diabetic foot infections who received treatment at Dow University Hospital in Karachi, Pakistan, conducted from June to December 2023.

The sample size was calculated using OpenEpi software. Two sets of patients were created: one with 80 infected patients and the other with 70 non-infected patients. Patients were included if they demonstrated symptoms of infection in diabetic foot and satisfied the American Diabetes Association's diagnostic criteria for diabetes. The existence of lesions below the ankle affecting the entire depth of the epidermis was defined as an infection of the diabetic foot, as well as symptoms such as abscesses, pain, redness, heat, swelling, cutaneous induration, and other signs of infection related to the infection.

Individuals who were immunosuppressed or taking immunosuppressive medications were excluded. Those with severe renal or liver disease, coagulation issues, consequences from malignant tumors, or illnesses of the organic nervous system were also not included. Additionally, disqualified were individuals having foot lesions from accidents. An uninfected diabetic foot exhibited no clinical evidence of infection.

After obtaining approval from the Dow University Hospital Ethical Board, patients meeting the inclusion and exclusion criteria and admitted to the diabetic ward were included in the study. Informed written consent was obtained from all participants.

A self-created survey instrument was employed to compile extensive patient data and clinical information. Age, gender, duration of the disease, presence of hypertension, coronary heart disease, history of smoking, and socioeconomic condition were among the questions. Glycated hemoglobin (HbA1c) levels determine glycemic management. The lipid profile (LDL-c, HDL-c, TG), hemoglobin levels, ESR, blood sugar levels, and other biochemical parameters were retrieved from the patient's medical records.

Various clinically diagnosed systemic risk factors were collected for analysis in the study, including peripheral neuropathy. This condition was assessed by testing for the absence of protective sensation in at least two out of three plantar forefoot locations using a 10-g monofilament test. Peripheral arterial disease (PAD) was identified by a toe systolic pressure measurement of less than 70 mmHg. Other risk factors, such as osteomyelitis, were confirmed using the Probe-to-Bone Test, where a sterile metal instrument was gently inserted into the ulcer; the detection of bone indicated a high likelihood of osteomyelitis. Diabetic retinopathy was diagnosed through a funduscopic exam based on the presence of microaneurysms, hemorrhages, and hard exudates.

Statistical Analysis

The data were analyzed using SPSS software. The Categorical variables between the two groups were analyzed using the Chi-square test. The student t-test was used to compare the means of continuous variables. To identify independent risk factors for diabetic foot infections, a multivariable logistic regression analysis was conducted, providing odds ratios (ORs) and 95% confidence intervals (CIs) to quantify the strength of association between each risk factor and diabetic foot infection.

RESULTS

Clinical characteristics and risk factors for diabetic foot infections are compared between two groups of patients: Group 1 (infected, n = 80) and Group 2 (uninfected, n = 70). The mean age of both groups is similar, with no significant difference observed (p = 0.587). The gender distribution is also comparable between the two groups, with a slightly higher percentage of males in both, although the difference is not statistically significant (p = 0.809). Significant differences are observed in systemic variables, including peripheral neuropathy, where Group 1 shows a higher prevalence (74.76%) compared to Group 2 (25.23%), with a statistically significant p-value of 0.001. Retinopathy is also more common in the infected group (75%) compared to the uninfected group (35.71%), with statistical significance (p < 0.001). Similarly, peripheral arterial disease (PAD) and osteomyelitis were more frequent in the infected group, with p-values of < 0.001 each. Additionally, smoking showed notable differences between the two groups, with higher percentages of smokers found in Group 1. (**Table I**)

Table I: Comparison of clinical data and risk factors among patients with diabetic foot infections

Variables	**All patients N=150**	**Group-1 (Infected) n=80**	**Group-2 (Uninfected) n=70**	***X2***	***p-value***
	n (%)	*n* (%)	*n* (%)		
Age (years)	57.11 ± 9.83	58.08 ± 8.24	57.41 ± 9.05	0.21	0.587
Gender					
Male	83 (55.33)	45 (56.25)	38 (54.29)	0.05	0.809
Female	67 (44.67)	35 (43.75)	32 (45.71)		0.124
Duration of DM (years)	11.35 ± 8.50	11.74 ± 8.53	11.23 ± 8.46	1.23	0.092
Hypertension					
Yes	72 (48.0)	38 (47.50)	34 (48.57)	0.06	0.743
No	78 (52.0)	42 (52.50)	36 (51.43)		
Peripheral neuropathy					
Yes	107 (71.33)	80 (74.76)	27 (25.23)	6.7	<0.001
No	43 (28.66)	25 (58.13)	18 (41.86)		
Retinopathy					
Yes	85 (56.66)	60 (75.00)	25 (35.71)	3.9	<0.001
No	65 (43.33)	20 (25.00)	45 (64.29)		
Peripheral arterial disease, *n* (%)					
Yes	72 (48.0)	50 (69.44)	22 (30.55)	5.7	<0.001
No	78 (52.0)	23 (29.48)	55 (70.51)		
Osteomyelitis					
Yes	77 (51.33)	49 (61.25)	28 (40.00)	4.0	<0.001
No	73 (48.66)	31 (38.75)	42 (60.00)		
Smoking					
Yes	60 (40.0)	38 (47.5)	22 (31.42)	7.5	<0.001
No	20 (13.33)	12 (15.0)	08 (11.42)		

X2= chi-square, p <0.001=significant

A multivariable logistic regression analysis investigating the risk factors associated with diabetic foot infection. It highlights that patients with peripheral arterial disease (PAD) are 3.1 times more likely to develop infections compared to those without PAD (OR = 3.1, 95% CI: 2.157–5.481, $p < 0.001$), demonstrating a statistically significant association. Additionally, neuropathy increases the odds of infection by 3.2 times (95% CI: 1.428–4.321, $p < 0.001$). Other significant independent risk factors include retinopathy (OR = 2.8, 95% CI: 1.873–4.957, $p < 0.001$), osteomyelitis (OR = 1.8, 95% CI: 1.057–3.264, $p < 0.001$), and smoking (OR = 2.0, 95% CI: 1.312–3.829, $p < 0.001$). These factors all contribute significantly to the risk of infection in diabetic foot patients. (**Table II**)

Table II: Multivariable logistic regression analysis

	Odd ratios	95% Confidence interval	*p*-value
PAD	3.1	2.157 5.481	<0.001
Neuropathy	3.2	1.428 4.321	<0.001
Retinopathy	2.8	1.873 4.957	<0.001
Osteomyelitis	1.8	1.057 3.264	<0.001
Smoking	2.0	1.312 3.829	<0.001

PAD: peripheral artery disease, p <0.001significant

A comparison of biochemical parameters between infected and uninfected groups reveals that high-density lipoprotein (HDL-c) levels are significantly lower in the infected group compared to the uninfected group (45±10 vs 55±15, $p = 0.049$), suggesting a potential link between lower HDL-c levels and diabetic foot infections. LDL-c levels are slightly higher in the infected group (190±35 vs 152±30), with a p-value of 0.032. Additionally, the infected group has a higher mean HbA1c (8.7±1.7 vs. 7.4±1.4, $p= 0.009$), indicating poorer long-term glucose control in patients with infections. (**Table III**)

Table III: Comparison of biochemical parameters between infected and uninfected groups

Biochemical Parameters	Group-1 (Infected) n=80	Group-2 (Un-infected) n=70	χ 2	*p*-value
HDL	45±10	55±15	4.57	0.049
LDL	190±35	152±30.	3.89	0.032
TG	150±50	130±40	2.76	0.097
Hb	9.41±1.31	9.67±1.04	2.99	0.071
Mean HbA1c	8.7±1.7	7.4±1.4	6.78	0.009
RBS	276±37.43	244±30.76	0.93	0.333

DISCUSSION

Diabetic foot infections are a frequent complication of diabetes, leading to increased morbidity and healthcare costs [17.] The current study reinforces previous findings that foot infections in diabetic patients are linked to both modifiable and non-modifiable risk factors.

The prevalence of diabetic foot infections in the sample population was notable, with eighty infected patients and seventy uninfected patients. Multivariate analysis identified three statistically significant independent risk factors for infections in diabetic foot, including smoking, neuropathy, and PAD.

Smoking contributes to vasoconstriction, reduced oxygen delivery, and delayed wound healing**,** all of which create an environment conducive to infection [18]. In a recent study, smoking consistently doubled the risk of foot infections (OR = 2, $p < 0.001$), consistent with a study conducted by Li T et al., who revealed that smoking is an independent risk factor for infection in diabetic foot (OR = 1.958; 95% CI, 1.015–3.777)[19]. Another study by Surya et al. concluded That Most patients were moderate smokers (27.5%), and the most common diabetic foot severity was Wagner Grade 3 (25%). Multivariable analysis showed a significant association between smoking status and diabetic foot severity ($p < 0.001$), highlighting smoking as a key factor in worsening foot infections [20]. Peripheral neuropathy emerged as another significant predictor of foot infection in our study. It is a common complication of diabetes that reduces foot sensation, making it difficult for patients to detect injuries. This delay in addressing minor wounds can lead to the development of ulcers and subsequent infections[21]. However, **Ponirakis G et al.** [22] negate our results and conclude that PNP is associated with ulcers but not with infections. Another study by **Pitocco et al.** [23] revealed that peripheral neuropathy increases the risk of diabetic foot infection (p = .0001).

Peripheral arterial disease was identified as a significant risk factor for diabetic foot infections in our study. Similarly, **Janbakhsh *et al.*** [24] reported a strong association between the prevalence of peripheral arterial disease and diabetic foot infections ($p = 0.041$). Osteomyelitis was strongly associated with foot infections, often developing as a result of untreated or poorly managed foot ulcers [25]. **Li et al.** [26] found a significant relationship between diabetic foot infections and osteomyelitis (p = 0.006). They emphasized that early intervention and aggressive treatment are crucial for preventing the spread of infection to the bone. The duration of diabetes approached significance (OR = 1.23, p = 0.09), suggesting that longer disease duration may be associated with a higher risk of foot infection. However, the association did not reach statistical significance.

The findings of lower HDL, higher LDL, and elevated HbA1c in the infected group are consistent with existing literature, which documents dyslipidemia and poor glycemic control as well-documented risk factors for diabetic foot infections. **Ikura *et al.*** [27] demonstrated that low HDL levels impair wound healing and increase the risk of infection, primarily due to the anti-inflammatory properties of HDL. Additionally, **Pei *et al.*** [28] highlighted that elevated LDL, associated with atherosclerosis, reduces blood flow to the lower extremities, further exacerbating the risk of infection. **Casadei *et al.*** [29] also found that poor glycemic control, as indicated by high HbA1c levels, is associated with a higher susceptibility to infections, as it impairs immune function in diabetic patients.

This study highlights the high incidence of foot infections in individuals with diabetes, even with intensive preventive measures. The study also highlights the significant risk of amputation associated with these infections. Fortunately, these risk factors can be identified through simple

screening foot examinations, allowing for targeted prevention. Effective interventions could substantially lower the incidence of these severe complications. Interventions should prioritize smoking cessation and neuropathy management, as these factors consistently emerged as significant predictors of infection. Tailored smoking cessation programs and early treatment of neuropathy could potentially reduce the incidence and severity of foot infections, leading to better patient outcomes. Additionally, routine screening for osteomyelitis and diabetic retinopathy in patients with foot ulcers may help identify those at higher risk of infection. Early detection and intervention in high-risk patients are crucial to preventing severe complications, such as amputation and prolonged hospitalization.

CONCLUSION

In conclusion, this study identifies several significant risk factors for diabetic foot infections, including smoking**,** peripheral neuropathy, and peripheral arterial disease**.** Targeting these risk factors through prevention strategies, early detection, and patient education can improve outcomes for diabetic patients and diminish the burden of infections in diabetic foot.

ABBREVIATIONS

HDL: High-density lipoprotein
LDL: Low-density lipoprotein
TG: Triglycerides
Hb: Hemoglobin
Mean HbA1c: Glycosylated Hemoglobin
RBS: Random Blood sugar
NP: Neuropathy
PAD: Peripheral artery disease
DM: Diabetes mellitus

Ethical permission: DOW University of Health Sciences, Karachi, Pakistan IRB letter No. IRB-2959/DUHS/Approval/2023/-88.
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AUTHOR CONTRIBUTION

Nazar S: Manuscript writing, literature review
Abbass SH: Manuscript writing, study design
Zaidi SS: Main idea, literature review, data analysis
Sandeelo N: Literature review, data interpretation
Hingorjo MR: Literature review, proofreading, final approval
Askari Z: Statistical Analysis, literature review

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