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Original Article

Association of Antioxidant, Inflammatory, and Glycemic Status in Patients with Diabetic Foot Ulcers in Karachi, Pakistan: A Comparative Cross-Sectional Study

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Abstract

Objective: To evaluate the association of antioxidant, inflammatory, and glycemic status in Patients with diabetic foot ulcers in Karachi, Pakistan.

Methodology: A comparative cross-sectional study was conducted at the Department of Physiology in collaboration with the Baqai Institute of Diabetology and Endocrinology, Baqai Medical University, Karachi, from June 2023 to June 2024. A total of 138 participants were enrolled and grouped into healthy controls, type 2 diabetics, and type 2 diabetics with foot ulcers. Type 1 diabetic patients were excluded. Glycemic parameters, including fasting blood glucose (FBG) and glycated hemoglobin (HbA1c), the oxidative stress marker superoxide dismutase (SOD), inflammatory biomarkers, including C-reactive protein (CRP), complete blood count parameters, and the neutrophil-to-lymphocyte ratio (NLR) were assessed. SOD was measured by ELISA, HbA1c by HPLC, and CRP by immunoturbidimetry. Statistical analysis was performed using IBM SPSS version 23.0.

Results: Median FBG, HbA1c, SOD, CRP, TLC, neutrophil percentage, lymphocyte percentage, and NLR differed significantly among the three groups by applying the Kruskal–Wallis test, and Dunnett's T3 post hoc analysis showed a significant difference ($p < 0.001$) in SOD levels among the three groups. HbA1c (OR=89.0; 95% CI:11.6–680), CRP (OR=1.08; 95% CI:1.02–1.13), and NLR (OR=1.86; 95% CI:1.28–2.71) were significant risk factors for DFU, whereas higher SOD levels (OR=0.87; 95% CI:0.84–0.91) showed a protective association by Multinomial logistic regression.

Conclusion: Poor glycemic control, increased systemic inflammation, and reduced antioxidant defense in DFU patients play a critical role in the development of foot ulcers in diabetic patients.

Keywords: C-reactive protein, diabetes mellitus, fasting blood sugar, foot ulcer, and superoxide dismutase.

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Introduction

Type 2 diabetes mellitus (T2DM) is a long-lasting metabolic condition characterized by insulin resistance or high blood sugar due to insufficient insulin synthesis.[1] Approximately 537 million people have T2DM currently, with projections indicating a sharp increase in the coming years. Estimates predict that by 2045, nearly 783 million individuals will be affected by diabetes worldwide. Foot ulcers are expected to occur at some point in the lives of about 15% of the 150 million persons worldwide with T2DM.[2] Inadequate control of hyperglycemia can lead to serious long-term complications in patients with T2DM.

The annual incidence of diabetic foot is approximately 2%, with lifetime prevalence ranging from 15% to 25% in patients with diabetes, and the burden of Diabetic foot ulcers (DFUs) in Pakistan, particularly, reported a pooled DFU prevalence of approximately 12.16% among patients with type 2 diabetes, with considerable variation across studies and an increasing prevalence of DFUs and lower-limb amputations in more recent years.[3,4] DFUs and lower-limb amputations are leading causes of

disability and mortality in patients with T2DM, both linked to infection or gangrene. Diabetic foot refers to sores on the foot caused by peripheral arterial disease in individuals with diabetic neuropathy and associated with the risk of osteomyelitis.[5]

The pathophysiology of DFUs is complex, primarily fueled by long-term oxidative stress, inflammation, and persistent hyperglycemia. Diabetic patients tend to have increased oxidative stress, which may ultimately cause tissue cell injury, impaired wound healing, and ulcer development. In DFU patients, increased serum pro-oxidant activity and decreased endogenous antioxidant defense activity, particularly superoxide dismutase (SOD), possibly due to glycation of the enzyme, increased oxidative consumption, and oxidative inactivation, leading to endothelial dysfunction, oxidative DNA damage with macrovascular and microvascular complications.[6] Elevated blood glucose, known as hyperglycemia, can lead to the generation of reactive oxygen species. This subsequently stimulates Protein Kinase C (PKC) and may interfere with ion channel regulation. Such developments are linked to the onset of diabetes-related complications.[7] The most widely used technique for determining blood sugar levels over 2–3 months is glycosylated hemoglobin (HbA1c), and considered a predictor of microvascular complications, including peripheral neuropathy.[8] Diabetic peripheral neuropathy is caused by oxidative stress in diabetic patients, due to the body's imbalance between pro-oxidants and antioxidants.

Acute-phase inflammatory markers play a vital role in the development of foot ulcers. Elevated levels of CRP reflect a marker of systemic inflammatory response that impedes angiogenesis and immune function, directly affecting wound healing in foot ulcers in diabetic patients.[6] Hyperglycemia and oxidative stress are associated with increased levels of intracellular adhesion molecule 1, pro-inflammatory cytokines, and chemokines, leading to chronic inflammation with leukocyte recruitment and a rise in neutrophil numbers or neutrophilia. The activation of innate immunity also triggers adaptive immunity, which includes lymphocytes that combat atherosclerosis and help control the inflammatory response. The neutrophil-lymphocyte ratio (NLR), i.e., an inflammatory marker, can be used to assess systemic inflammatory conditions in diabetic foot ulcer patients. Increased NLR and CRP levels, along with lower SOD levels, are observed in diabetic foot ulcer patients.[9]

Most Pakistani studies on DFUs have been done on the evaluation of prevalence, risk factors, foot-care practices, and mode of infection. Despite the increasing evidence regarding inflammatory and oxidative biomarkers, limited local data from Pakistan has simultaneously evaluated the interrelated biological pathways in the development of foot ulcers or evaluated glycemic, inflammatory, and antioxidant status in T2DM with and without foot ulcer in the local population of Karachi. Therefore, the present study was undertaken to evaluate the association between antioxidant status, inflammatory status, and glycemic status in patients with diabetic foot ulcers (DFUs) in Karachi, Pakistan.

Methodology

This cross-sectional comparative study was conducted by Physiology Department in collaboration with the Baqai Institute of Diabetology and Endocrinology (BIDE), Baqai Medical University, Karachi. The study was carried out over one year from June 2023 to June 2024. Approval from the Ethical Review Committee (BMU-EC/01-2023), Baqai Medical University, Karachi, Pakistan on July 12, 2023. The study adhered to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to their enrollment, and confidentiality of data was strictly maintained throughout. The sample size was calculated using Effect size OpenEpi online software, a confidence level of 95%, a significance level (α) of 1%, and adequate statistical power were assumed. The calculated minimum sample size was 138 participants, who were equally distributed into three groups (n = 46 per group). This sample size was considered adequate to detect significant differences among groups.[10,11] A purposive (non-probability) sampling technique was employed. A total of 138 participants were enrolled and categorized into three groups: Group 1 (Control): Healthy individuals (n = 46), Group 2: T2DM without foot ulcers (n = 46), Group 3: T2DM with foot ulcers (n = 46). Patients with type 2 diabetes mellitus of more than five years' duration, with or without ischemic or neuropathic foot ulcers, were included. The control group consisted of healthy individuals with normal fasting blood glucose (FBG) and HbA1c levels. Inclusion criteria included adult participants of either sex who voluntarily consented to participate. Exclusion criteria were: History of deep vein thrombosis (DVT), Insulin-dependent diabetes mellitus, Foot or leg ulcers due to trauma or non-diabetic causes, Acute or chronic inflammatory diseases unrelated to diabetes. A detailed physical examination was performed, and demographic, clinical, medical, and surgical histories were recorded using a standardized proforma. Venous blood samples were drawn in the

morning after an overnight fast of 8–10 hours. Samples were drawn into Plain tubes for biochemical analysis. EDTA-containing tubes for complete blood count (CBC) analysis. HbA1c was measured by High-Performance Liquid Chromatography (HPLC) using a Lifotronic analyzer. Complete blood count (CBC) was analyzed using a Celltac K automated Coulter counter. Superoxide dismutase (SOD) levels was evaluated through the enzyme-linked immunosorbent assay (ELISA) method by BT Lab. C-reactive protein (CRP) levels were assessed using immunoturbidimetric analysis on the Indiko™ Thermo Fisher Scientific system, Finland. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute number of neutrophil by the number of lymphocyte. Data entry and statistical analysis were carried out using predefined criteria to minimize analytical bias. Using IBM SPSS version 23.0, data analysis was performed. The normality of continuous variables was assessed using the Shapiro–Wilk test. As fasting blood FBG, HbA1c, SOD, CBC parameters, and CRP were not normally distributed, they are presented as median with interquartile range (IQR; 25th–75th percentile). Comparisons among the three study groups were analysed using the Kruskal–Wallis test. For variables showing a statistically significant overall difference, Dunnett's T3 post hoc test was used for pairwise comparisons. Multinomial logistic regression analysis was performed to identify independent predictors of T2DM and DFU, with the healthy control group as the reference category. The strength of associations was described as odds ratios (ORs) with 95% confidence intervals (95% CIs). A two-tailed p-value < 0.05 was considered statistically significant for all analyses.

Results

Table 1 -The median of FBG and HbA1c increased progressively from healthy controls to T2DM and DFU patients (p<0.001). Conversely, SOD levels declined significantly across the three groups, indicating progressive impairment of antioxidant defense. CRP, WBC count, neutrophil percentage, and NLR were highest in the DFU group, whereas lymphocyte percentage was significantly lower ($p < 0.01$) for all parameters by using the Kruskal–Wallis test.

Table 2 presents the post hoc analysis using Dunnett T3, which revealed that: FBG and HbA1c were significantly increased in both T2DM groups (with and without foot ulcers) compared with normal healthy group ($p < 0.001$), CRP levels were significantly increased in T2DM with foot ulcer group compared with both healthy controls and T2DM without ulcers ($p < 0.001$), SOD levels differed significantly among all included groups ($p < 0.001$), confirming a stepwise reduction in antioxidant defense with disease progression, TLC was significantly elevated in T2DM patients with foot ulcers compared with controls ($p = 0.025$), Neutrophil percentage and NLR were significantly higher, and lymphocyte percentage (L%) significantly lower, in the foot ulcer group compared with both other groups ($p < 0.01$). Table 3 presents the multinomial logistic regression analysis identifying independent predictors of T2DM and diabetic foot ulcers. Higher FBG, HbA1c, and WBC count were significantly associated with increased odds of T2DM {[OR = 1.06; 95% CI: 1.03–1.10], [OR = 72.6; 95% CI: 9.56–552], [OR = 1.44; 95% CI: 1.16–1.78]} whereas In contrast, SOD showed a protective (negative) association with T2DM [OR = 0.91; 95% CI: 0.88–0.94] respectively. Among patients with DFU group, elevated FBG, HbA1c, CRP, WBC count, neutrophil percentage, and NLR were significant positive predictors {[OR = 1.06; 95% CI: 1.03–1.09], [OR = 89.0; 95% CI: 11.6–680], [OR = 1.08; 95% CI: 1.02–1.13], [OR = 1.47; 95% CI: 1.18–1.82], [OR = 1.09; 95% CI: 1.04–1.15], and [OR = 1.86; 95% CI: 1.28–2.71]} respectively while higher SOD and lymphocyte percentage were negatively associated {[OR = 0.87; 95% CI: 0.84–0.91], and [OR = 0.88; 95% CI: 0.83–0.94] } respectively indicating protective effects. All reported associations were statistically significant ($p < 0.05$).

Discussion

The pathogenesis of DFUs is complex, primarily associated with long-term inflammation, oxidative stress, and hyperglycemia in diabetic patients. Elevated serum pro-oxidants, decreased serum antioxidants (SOD), and elevated levels of inflammatory markers (CRP and NLR) support this association.[12] We observed significant differences in HbA1c levels among groups ($p < 0.05$; see Table 1). A study carried out in Pakistan reached a similar conclusion by Nizamud Din et al.[13]

HbA1c levels showed a strong association [OR=72.6* (C. I=9.56-552)] with the onset of diabetes in healthy individuals (see Table 3). Furthermore, Table 3 shows a strong association of HbA1c with the incidence of diabetic foot ulcers [OR=89.0* (C. I=11.6-680)].[14]

A meta-analysis by Tang et al. reported that HbA1c levels are an independent predictor of diabetic foot

Table 1: *Comparison of antioxidant, inflammatory, and glycemic parameters across groups*

Parameters	Healthy group n-46	T2DM group n-46	T2DM with foot ulcer group n-46	p-value
FBS (70-99mg/dl)	86(80-91)	149.5 (119-200)	118 (92-184)	<0.01*
HbA1c (<5.7%)	5.4(5.2-5.6)	8.45 (7.2-10.1)	9.8 (7.6-10.9)	<0.01**
C-Reactive Protein(<10mg/L)	5(4-7)	5(4-10)	35(10-89)	<0.01*
Superoxide Dismutase(2-5U/ml)	167.75 (156.2-185.36)	106.2 (94.75-122.71)	67.07 (48.05-80.7)	<0.01**
White blood cells (4000-11000 cells/uL)	6.4(5.6-7.3)	6.95(6-8)	9.3(7.4-13)	<0.01*
N% Count (40-70%)	67(60-71)	66.5(60-70)	72(67-81)	<0.01*
L% Count (20-30%)	30(25-36)	29.5(25-36)	23(15-29)	<0.01*
'Neutrophil-to-Lymphocyte Ratio (NLR) (1.0 – 3.0 ratio)	2.23(1.67-2.84)	2.24(1.69-2.8)	3.13(2.31-5.33)	<0.01*

*p<0.05 was considered statistically significant findings, and **p-value <0.05 suggests statistical significance in post hoc analysis.*

ulcers (DFUs).[15] Poor glycemic management raises the risk of chronic foot ulcers, which ultimately leads to lower-limb amputations as a complication in type 2 diabetic patients. Conversely, good glycemic control is pivotal for decreasing the incidence of amputation or limb loss in T2DM patients.[16,6] HbA1c significantly contributes to the overproduction of superoxide anions and hydroxyl radicals.[6] These reactive oxygen species (ROS) can cause various cellular injuries. The findings of the present investigation observed significant differences ($p < 0.05$) in SOD concentrations across all three groups, as shown in Table 2. SOD levels displayed a strong association with a diminished possibility of developing diabetes [OR=0.91* (C. I=0.88-0.94)], suggesting protective advantages for the healthy group, as shown in Table 3. Moreover, participants with T2DM showed a lower chance or protective association [OR=0.87* (C. I=0.84-0.91)] of encountering foot ulcers (Table 3). Mossanda et al. indicated that individuals with diabetes and diabetic foot ulcers displayed decreased SOD activity compared to the healthy group (group 1).[17] Additionally, Vairamon et al. observed a gradual reduction in overall antioxidant activity in both T2DM (group 2) and patients with foot ulcers (group 3), corroborating their research outcomes ($p < 0.01$).[18] However, a Nigerian study reported non-significant results ($P > 0.05$) contrary to our observations.[19]

In addition, we observed non- considerable differences ($p > 0.903$) in median CRP levels among healthy individuals and type 2 diabetics (Table 2). Consistent with our findings, other studies have shown non-significant differences ($p > 0.05$).[20] Elevated CRP levels are linked to a higher risk of T2DM [OR=1.04 (C. I=0.99-1.10)]; see Table 3, and they also indicate a higher chance of foot ulcer development in type 2 diabetic patients (DFUs) [OR=1.08* (C. I=1.02-1.13)]; see Table 3. Increased concentrations of CRP, an inflammatory marker, may

Table 3: *Antioxidant, inflammatory, and glycemic status among study groups: risk estimation for diabetic and diabetic foot ulcer patients using multinomial logistic regression analysis.*

Parameters	Odds Ratio in T2DM group with C.I 95%	Odds Ratio in T2DM with foot ulcer group C.I 95%
Fasting Blood sugar mg/dl level	1.06* (C.I =1.03-1.10)	1.06* (C.I =1.03-1.09)
HbA1c level	72.6* (C.I =9.56-552.)	89.0* (C.I =11.6-680.)
C-reactive protein level	1.04 (C.I =0.99-1.10)	1.08* (C.I =1.02-1.13)
Superoxide dismutase level	0.91* (C.I =0.88-0.94)	0.87* (C.I =0.84-0.91)
White blood cells	1.44* (C.I =1.16-1.78)	1.47* (C.I =1.18-1.82)
N (%)	1.00 (C.I =0.96-1.05)	1.09* (C.I =1.04-1.15)
L (%)	0.99 (C.I =0.94-1.04)	0.88* (C.I =0.83-0.94)
Neutrophil-to-Lymphocyte Ratio (NLR)	1.20 (C.I =0.81-1.76)	1.86* (C.I =1.28-2.71)

** p<0.05- significant odds ratio*

Table 2: *Multiple comparisons of antioxidant, inflammatory, and glucose status between groups of study*

Variable(s)	Comparison of		Mean Difference	S.E	Confidence Interval(95%)		p-value
					Lower Bound	Upper Bound	
Fasting blood sugar (mg/dl)	T2DM	DFUs	12	18	-31.7	55.8	0.877
	Control	T2DM	-79.5	11.4	-107.6	-51.5	0.001*
	Control	DFUs	-67.5	14.2	-102.6	-32.4	0.001*
HbA1c	T2DM	DFUs	-0.9	0.4	-1.9	0.2	0.142
	Control	T2DM	-3.2	0.3	-4	-2.5	0.001*
	Control	DFUs	-4.1	0.3	-4.9	-3.3	0.001*
C-Reactive Protein	Control	Diabetic	-5	11.6	-32.5	22.5	0.903
	Control	DFUs	-67.3	11.6	-95	-39.6	0.001*
	Diabetic	DFUs	-62.3*	11.6	-90	-34.6	0.001*
Superoxide Dismutase	Control	Diabetic	64.7*	5.6	51.3	78.2	0.001*
	Control	DFUs	98.5*	5.6	85.1	112	0.001*
	Diabetic	DFUs	33.7*	5.6	20.3	47.2	0.001*
White blood cells/TLC	Control	Diabetic	-2.7	1.5	-6.4	0.9	0.186
	Control	DFUs	-4.1*	1.5	-7.8	-0.4	0.025
	Diabetic	DFUs	-1.3	1.5	-5	2.2	0.643
Neutrophils Count %	Control	Diabetic	-0.73	1.9	-5.4	3.9	0.927
	Control	DFUs	-7.5*	2	-12.2	-2.7	0.001*
	Diabetic	DFUs	-6.7*	1.9	-11.5	-2	0.002*
Lymphocytes count %	Control	Diabetic	0.4	1.7	-3.7	4.6	0.965
	Control	DFUs	7.8*	1.7	3.6	12	0.001*
	Diabetic	DFUs	7.4*	1.7	3.2	11.6	0.001*
'Neutrophil-to-Lymphocyte Ratio (NLR)	Control	Diabetic	-0.2166	0.39583	-1.1548	0.7216	0.848
	Control	DFUs	-1.74996*	0.398	-2.6933	-0.8066	0.001*
	Diabetic	DFUs	-1.53335*	0.39583	-2.4716	-0.5951	0.001*

**p<0.05 was considered statistically significant using Dunnett T3*

suggest an increased risk of T2DM and foot ulcer development in T2DM patients, reinforcing the connection between inflammation and the underlying mechanisms in the pathogenesis of diabetes and foot ulcer.[21] The findings of our research demonstrate that diabetic patients with foot ulcer complications have significantly higher neutrophil counts and NLR values than type 2 diabetic patients without complications (Table 3). Vujčić and others observed comparable results. An assessment of the NLR may serve as a diagnostic tool for forecasting the incidence of DFU and could function as a biomarker for risk assessment of lower-limb amputation. Multiple recent studies confirm that elevated NLR is significantly associated with ulcer severity, delayed wound healing, and risk of amputation, outperforming CRP in prognostic value.[22,23] Diabetic foot ulcers represent a more advanced inflammatory and oxidative state rather than a consequence of hyperglycemia alone. Chronic inflammation is considered one of the key pathophysiological mechanisms underlying the development of diabetic complications.[24] As currently proposed, these biochemical markers could play a significant role in diagnostic, prognostic, and predictive value in the incidence of complications in diabetic patients, which is associated with simultaneous infections or sepsis, along with the likelihood of lower-limb amputation and post-surgical morbidity or mortality.[12] It is Cross-sectional design prevents causal inference, with single-center study limits generalizability, the sample size was relatively small,

and only one SOD antioxidant was evaluated.

Conclusion

These findings suggest that chronic inflammation and increased oxidative stress are key drivers of foot ulcer development in T2DM patients beyond hyperglycemia alone. SOD demonstrated a protective association, whereas HbA1c, CRP, and NLR emerged as significant predictors of DFU in T2DM patients.

Recommendations:

1. Conduct genetic research on SOD.
2. Increase sample size of the study.
3. Furthermore, timely detection of risk factors in individuals with diabetes is essential for preventing foot ulcers and delaying limb amputations.

Ethical Approval: The IRB/EC approved this study via letter no. Ref. BMU-EC/01/2023, dated February 23, 2023.

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Authors' Contribution

SUA: Conception.

QS, RAS: Design of the work.

UT,JL,BZ: Data acquisition, analysis, or interpretation.

QS,UT,JL,BZ: Draft the work.

SUA,RAS: Review critically for important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

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