

Original article

The potential impact and diagnostic value of inflammatory markers on diabetic foot progression in type II diabetes mellitus: A case-control study



Amal Ahmed Mohamed^a, Mona Abd Elmotaleb Hussein^b, Ihab Nabil Hanna^c, Abdulqadir Jeprel Japer Nashwan^{d,*}, Mohamed Saleh^e, Wafaa Yousif Abdel Wahed^f, Asmaa Mohamed Mohamed Mansour^g, Mohamed Ramadan Ezz Al Arab^h, Naglaa Fawzyⁱ, Yasser Sakrⁱ, Hassan Shalby^j, Eman AlHussain^k, Marwa Kamal Darwish^l, Heba El-Osaily^m, Mervat Naguibⁿ, Ahmed Ali Mohamed^o, Waleed Farouk Mohamed^p, Wael Hafez^q

^a Biochemistry Department, National Hepatology and Tropical Medicine Research Institute, Gothi, Egypt

^b Internal Medicine Department, National Institute of Diabetes and Endocrinology, Egypt

^c Surgical Department, National Institute of Diabetes and Endocrinology, Egypt

^d Hamad Medical Corporation, P.O. Box 3050, Doha, Qatar

^e Gastroenterology Department, National Hepatology and Tropical Medicine Research Institute, Egypt

^f Public Health and Community Medicine, Faculty of Medicine, Fayoum University, Egypt

^g Biochemistry Department, Faculty of Science, Fayoum University, Egypt

^h Hepatology and Gastroenterology Department, Ahmed Maher Teaching Hospital, Egypt

ⁱ Clinical and Chemical Pathology Department, National Institute of Diabetes and Endocrinology, Egypt

^j Internal Medicine Department, Faculty of Medicine, Misr University for Science and Technology, Egypt

^k Clinical and Chemical Pathology Department, Faculty of Medicine, Cairo University, Egypt

^l Chemistry Department (Biochemistry Branch), Faculty of Science, Suez University, Suez 43518, Egypt

^m Biochemistry Department, Faculty of Pharmacy, Ahram Canadian University, Egypt

ⁿ Internal Medicine Department, Faculty of Medicine, Cairo University, Egypt

^o Intensive Care Unit, Theodor Bilharz Research Institute, Giza, Egypt

^p Healthpoint Hospital, Abu Dhabi, United Arab Emirates

^q Internal Medicine Department, National Research Centre, Elbohoos Street, Dokki, Giza, Egypt

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ABSTRACT

Background: The wound-healing process in diabetic foot is affected by pro and anti-inflammatory markers, and any disruption in the inflammatory reaction interferes with tissue homeostasis, leading to chronic non-wound healing.

Aim: This study aimed to determine the diagnostic value and effect of CRP, IL-6, TNF, and HbA1c on initiation and progression of diabetic foot ulcers.

Method: ELISA was used to quantify IL-6, TNF, CRP, and HbA1c in 205 patients with diabetes, and 105 were diabetic foot free. The prevalence and progression of diabetic foot were also evaluated. The area under the curve (AUC) was calculated using the receiver operating characteristic (ROC) curve to analyze the predictive values. Forward stepwise logistic regression analysis was used to compute the odds ratio (OR) and the corresponding 95% confidence intervals (CIs).

Results: CRP, IL-6, and FBS were found to be significant predictors of diabetic foot (OR = 1.717, 95% CI = 1.250–2.358, $P = 0.001$; OR = 1.434, 95% CI = 1.142–1.802, $P = 0.002$; and OR = 1.040, 95% CI = 1.002–1.080, $P = 0.037$), respectively. The AUCs for CRP, IL-6, and HbA1c in predicting diabetic foot were 0.839, 0.728, and 0.834, respectively, demonstrating a good predictive value for each diagnostic marker.

Conclusion: The current study demonstrated that IL-6, CRP, and HbA1c may be useful biomarkers to indicate diabetic foot progression. Furthermore, our findings showed a substantial relationship between CRP and HbA1c in individuals with diabetic foot conditions.

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* Corresponding author.

E-mail address: anashwan@hamad.qa (A.J. Japer Nashwan).

Impacto potencial y valor pronóstico de los marcadores inflamatorios en la progresión del pie diabético en diabetes mellitus tipo II. Un estudio de casos y controles

R E S U M E N

Palabras clave:

Diabetes
PCR
TNF
IL-6
Úlcera del pie
Citocina inflamatoria
HbA1C

Antecedentes: Dado que los marcadores inflamatorios pueden influir en la capacidad del pie diabético para curar heridas, la interrupción de la respuesta inflamatoria puede dar lugar a una ausencia de curación crónica de las heridas.

Objetivo: Determinar el valor predictivo de PCR, IL-6, TNF y HbA1C en la identificación de úlceras de pie diabético y su progresión.

Método: Se utilizó el método ELISA para cuantificar IL-6, TNF, PCR y HbA1C en 205 diabéticos, y 105 no tenían pie diabético. Se evaluó la prevalencia y la progresión del pie diabético.

Resultados: Se observó un marcado aumento en CRP, HbA1C e IL-6 entre las personas con pie diabético. Los OR para PCR, IL-6 y HbA1C: 1,359 (IC 95% = 1,189–1,554, p = 0,001), 1,245 (IC 95% = 1,091–1,420, p = 0,001) y 1,866 (IC 95% = 1,238–2,814, p = 0,003), respectivamente. Las áreas bajo la curva para CRP, IL-6 y HbA1C en la predicción del pie diabético fueron 0,839, 0,728 y 0,834, respectivamente, lo que demuestra un buen valor predictivo para cada marcador de diagnóstico.

Conclusión: El presente estudio demostró que IL-6, CRP y Hb A1C pueden ser biomarcadores útiles para el pronóstico del pie diabético. Además, nuestros hallazgos muestran una relación sustancial entre PCR y Hb A1C para personas con pie diabético.

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Introduction

Diabetes mellitus (DM) is associated with morbidity and mortality. This condition is classified as a metabolic disorder, which is characterized by elevated levels of glucose in the blood-stream. Diabetes mellitus has a variety of complications, including microvascular and macrovascular diseases.¹ Neuropathy is considered to be the most severe complication of microvascular diseases, and diabetic foot ulcers are one of the most common complications. The global prevalence and incidence of diabetes mellitus have increased, leading to the recognition of diabetic foot as a disease that poses a significant burden on a global scale. Foot ulcers in individuals with diabetes can cause significant harm to the underlying tissues, including damage to nerves and blood vessels.²

The occurrence of foot ulcers is attributed to multiple factors, including alterations in the bone anatomy of the foot, neuropathy, and atherosclerosis. Such factors are observed more frequently in individuals with diabetes, as reported in several studies.^{3,4} According to a reliable source,⁵ diabetic foot ulcers result in a greater number of hospitalizations than any other complication associated with diabetes.

The formation of persistent wounds is an obstacle for the immune system. The wound healing process is significantly influenced by anti-inflammatory and pro-inflammatory cytokines, and any disruption of the immune system can result in non-healing of the diabetic foot. This has been documented in literature.⁶ Inflammatory markers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tissue necrosis factor (TNF), modulate insulin signaling pathways, causing insulin resistance and type II diabetes. A previous study found a positive relationship between elevated CRP levels and the incidence of diabetes mellitus incident.⁷

Prolonged elevation of blood glucose levels results in increased macrophage generation, thereby augmenting the secretion of TNF and cytokines, resulting in the development of insulin resistance among individuals with diabetes.⁸ The cytokines TNF- and IL-6 are vital for the advancement of diabetic foot, as documented in previous research.⁹ Furthermore, it was observed that the CRP is primarily secreted through the influence of IL-6 and TNF. The interrelationships among these biomarkers have been elucidated in various studies.^{7,10} However, the diagnostic significance of this finding remains unclear.

Glycosylated hemoglobin (HbA1c) is considered a primary indicator for the surveillance of blood glucose levels. The method in question is a means of monitoring blood glucose levels in diabetes, and provides insight into the levels of glucose in the bloodstream over an extended period of time, typically spanning several weeks. This approach is widely regarded as the most critical method for monitoring the blood glucose levels.¹¹ Elevated levels of HbA1c have the potential to serve as prognostic indicators for the onset of peripheral neuropathy.⁹ Therefore, in this study, we examined the diagnostic value of IL-6, CRP, TNF, and HbA1c as of diabetic foot progression in patients with DM.

Materials and methods

This study enrolled 205 patients with diabetes from the outpatient department of the Diabetes and Endocrinology National Institute in Egypt. The present study underwent an ethical review and received approval from the ethics department of (General Organization of Teaching Hospitals and Institutions). The selection of participants was based on their clinical, biochemical, and serological characteristics. The study design was a case-control study; the study population was stratified into two distinct cohorts: diabetic foot ulcer cohort ($n=100$) and diabetic control cohort ($n=105$). The patients in the case group were diabetic patients who were clinically diagnosed with diabetic foot ulcers, whereas the diabetic control group included diabetic patients clinically diagnosed as free of diabetic foot ulcer, matching the case group. Patients without diabetes were excluded from this study.

Laboratory analysis

A sample of 5 ml of venous blood was collected. Fasting glucose, random glucose, total cholesterol, high-density lipoproteins, triglycerides, urea, and creatinine levels were measured using an Olympus AU400 analyzer (Olympus, Tokyo, Japan), an automated biochemistry analyzer. Complete blood count was analyzed using an automated Coulter Counter, while the inflammatory markers CRP, TNF, and IL-6 were measured using enzyme-linked immunosorbent assay (ELISA). The concentrations of these items were measured using an ELISA reader (Stat Fax 3300; Awareness Technologies, FL, USA) according to the manufacturer's instructions.

Table 1

Demographic, clinical, and laboratory data of patients in the diabetic foot and diabetic control patients' groups.

Variables	Diabetic foot ulcer patients (<i>n</i> = 100)	Diabetic control patients (<i>n</i> = 105)	<i>P</i> -value
Sex F/M, <i>n</i> (%)	39 (39%)	44 (41.9%)	0.672
Age (years)	48.24 ± 12.316	48.30 ± 10.304	0.972
BMI (kg/m ²)	29.31 ± 4.8	28.03 ± 4.7	0.057
CBC			
WBC (cell/μL)	10008.00 ± 7.35	3215.891 ± 4.35	<0.001
MCH	30.483 ± 3.35	31.248 ± 2.16	0.053
Lymphocytes (cell/μL)	23.821 ± 4.2027	36.810 ± 6.8600	<0.001
HbA1c (%)	7.068 ± 1.64	4.867 ± 1.66	<0.001
FBS (mg/dL)	160.95 ± 45.219	129.33 ± 20.220	<0.001
PP (mg/dL)	251.40 ± 72.112	166.89 ± 34.419	<0.001
INR	1.18 ± 0.13	1.06 ± 0.089	<0.001
Creatinine	1.01 ± 0.19	0.96 ± 0.16	0.039
Urea (mmol/L)	34.79 ± 10.67	29.31 ± 8.44	<0.001
Cholesterol	172.78 ± 41.0	148.19 ± 18.4	<0.001
TG (mg/dL)	189.8 ± 24.7	147.3 ± 22.96	<0.001
HDL (mg/dL)	32.98 ± 9.9	43.7 ± 8.5	<0.001
LDL (mg/dL)	126.75 ± 27.8	107.8 ± 10.8	<0.001
TNF (ng/mL)	31.49 ± 12.34	26.7 ± 4.44	<0.001
IL-6 (pg/mL)	28.36 ± 9.7	20.78 ± 5.8	<0.001
CRP (ng/mL)	17.4 ± 12.4	5.19 ± 3.35	<0.001
Grade of ulcer		–	–
1	50 (50.0%)		
2	26 (26.0%)		
3	24 (24.0%)		

Data were means ± SD or proportions for categorical variables. WBCs, white blood cells; MCH, mean corpuscular hemoglobin; HbA1c, glycosylated hemoglobin; FBG, fasting plasma glucose; PP, postprandial blood glucose; INR, International Normalized Ratio; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; TNF, tumor necrosis factor; IL-6, interleukin 6; CRP, C-reactive protein.

Statistical analysis

The data required for the study were collected and verified for precision prior to being encoded and subjected to analysis using SPSS software version18. Basic descriptive statistics, such as means and standard deviations, were computed for quantitative data, whereas qualitative data were presented using numerical values and percentages. The statistical analysis involved the utilization of the *t*-test to assess qualitative data from cases and controls, and the chi-square test to compare qualitative variables. Correlation coefficient (*r*) was used to denote Pearson's correlation. Multiple regression analysis was employed to identify predictors. A receiver operating characteristic (ROC) curve was developed to assess the efficacy of a marker in detecting cases. The sensitivity and specificity were evaluated at predetermined thresholds. A significance level of 0.05 was deemed appropriate for determining statistical significance.

Results

Demographic, clinical, and laboratory characteristics

The study cohort was stratified into two distinct groups: a diabetic foot group and a non-diabetic foot group. The groups were subsequently evaluated based on demographics, such as sex, age, and BMI. The sex distribution did not differ significantly between the groups (*P* = 0.6). The mean age of the group of patients with diabetic foot was 48.24 ± 12.316 years, whereas the mean age of the diabetic control group was 48.30 ± 10.304 years. No evident differences were observed between the groups. The diabetic foot group exhibited non-significantly elevated BMI compared to the diabetic control group, as indicated in Table 1.

The study found that the levels of WBC, creatinine, and urea were noticeably elevated in the diabetic foot group. The study findings indicated that the levels of HbA1c, postprandial blood glucose, and CRP were significantly elevated in the diabetic foot group compared to those in the diabetic control group. The study findings

indicated that the diabetic foot group exhibited elevated levels of LDL, triglycerides, and total cholesterol compared to the diabetic control group. Furthermore, the levels of HDL, MCH, FBG, and lymphocytes were significantly decreased (Table 1).

Association of diabetic foot with some independent factors

Forward stepwise logistic regression analysis was used to ascertain the predictors of diabetic foot. The results revealed that high levels of FBS, IL-6, CRP, and TG were significantly associated with diabetic foot with odds ratios of OR = 1.04; 95% CI 1.002–1.080, OR = 1.43; 95% CI 1.142–1.802, OR = 1.71; 95% CI 1.25–2.35 and OR = 1.10; 95% CI 1.045–1.16, respectively. In contrast, high levels of HCT and HDL were significantly associated with protection against diabetic foot, as shown in Table 2.

Correlation analysis

The results indicated a noteworthy positive correlation between TNF and IL-6 [*r* = 0.767, *P* = 0.00] and urea [*r* = 0.587, *P* = 0.001]. A negative correlation was observed between TNF and MCH (*r* = -0.194, *P* = 0.053) and lymphocytes (*r* = -0.205, *P* = 0.041). The results indicated a significant positive correlation between IL-6 and urea (*r* = 0.483, *P* = 0.001), as well as significant negative correlations between IL-6 and both WBC (*r* = -0.206, *P* = 0.039) and RBC (*r* = -0.199, *P* = 0.047). The results indicated that there was a statistically significant positive correlation between CRP and various biomarkers, including HbA1c (*r* = 0.226, *P* = 0.24), MCV (*r* = 0.205, *P* = 0.041), LDL (*r* = 0.406, *P* = 0.001), TC (*r* = 0.447, *P* = 0.001), and TG (*r* = 0.342, *P* = 0.001). Additionally, HbA1c levels were significantly positively correlated with FBG [*r* = 0.637, *P* = 0.001], PP [*r* = 0.661, *P* = 0.001], creatinine [*r* = 0.260, *P* = 0.009], and RBC [*r* = 0.308, *P* = 0.002], as presented in Table 3. The findings suggest a lack of statistically significant correlation between ulcer severity, ulcer size, and infection with CRP, IL-6, and HbA1c in individuals with diabetic foot, as presented in Table 4.

Table 2

Forward stepwise logistic regression analysis predictors of diabetic foot.

Predictors	B	P value	OR	95% CI for OR	
				Lower	Upper
FBS	0.040	0.037	1.040*	1.002	1.080
IL-6	0.361	0.002	1.434*	1.142	1.802
CRP	0.540	0.001	1.717*	1.250	2.358
HCT	-0.472	0.001	0.624*	0.468	0.831
TG	0.099	0.000	1.104*	1.045	1.167
HDL	-0.228	0.005	0.796*	0.678	0.934
Constant	-9.109	0.126	0.000		

P and r values were calculated using Pearson correlation test at 95% confidence intervals. *P<0.05.

Table 3

Correlation coefficients of CRP, IL-6, TNF, and HbA1c with clinical risk factors of diabetic foot patients.

	TNF	IL-6	CRP	HbA1c	FBS	PP	Creatinine	Urea	RBC	WBC	MCV	MCH	Lymphocyte	Chol	TG	LDL	
<i>TNF</i>																	
R	1	0.767**	0.083	-0.113	0.130	0.014	-0.044	0.587**	-0.112	-0.095	0.020	-0.194	-0.205*	0.053	0.016	0.090	
P-value		0.000	0.412	0.262	0.197	0.889	0.663	0.000	0.265	0.345	0.843	0.053	0.041	0.600	0.873	0.373	
<i>IL-6</i>																	
R	0.767**	1	0.101	-0.111	0.012	-0.005	-0.002	0.483**	-0.199*	-0.206*	0.126	0.000	-0.123	0.052	0.033	0.095	
P-value		0.000		0.315	0.272	0.909	0.964	0.982	0.000	0.047	0.039	0.210	0.997	0.224	0.610	0.743	0.348
<i>CRP</i>																	
R	0.083	0.101	1	0.226*	0.102	0.133	-0.148	-0.169	0.135	0.006	0.205*	-0.060	0.031	0.447**	0.342**	0.406**	
P-value		0.412	0.315		0.024	0.312	0.186	0.141	0.092	0.181	0.951	0.041	0.556	0.760	0.000	0.001	0.000
<i>HbA1c</i>																	
R	-0.113	-0.111	0.226*	1	0.637**	0.661**	0.260**	-0.008	0.308**	0.078	-0.057	-0.206*	0.186	0.164	-0.037	0.075	
P-value		0.262	0.272	0.024		0.000	0.009	0.939	0.002	0.440	0.572	0.040	0.064	0.104	0.715	0.456	

P and r values were calculated using Pearson correlation test at 95% confidence intervals.

* P<0.05.

** P<0.001.

Table 4

The correlation of diabetic foot ulcer grade, size infection with TNF, CRP, and HbA1c.

Diabetic foot	IL-6		TNF		CRP		HbA1C	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<i>Grades of ulcer</i>								
1	28.33	8.841	31.72	12.833	20.0684	14.36821	7.080	1.5426
2	31.23	11.255	34.27	13.012	13.3431	8.26010	6.727	1.8205
3	25.33	9.211	28.00	9.996	16.3208	12.80007	7.413	1.6308
P value		0.100		0.198		0.085		0.399
<i>Size of ulcer</i>								
<4 cm	28.67	9.106	30.65	10.478	17.6910	11.56715	6.971	1.4230
≥4 cm	28.04	10.434	32.37	14.093	17.1388	14.21868	7.169	1.8499
P value		0.747		0.489		0.831		0.547
<i>Bacterial infection</i>								
Osteomyelitis	26.43	9.209	23	29.22	17.5522	13.33386	7.774	1.8543
Subcutaneous	28.33	9.993	45	31.47	16.3422	11.19711	6.840	1.3864
Superficial	29.79	9.791	32	33.16	18.8419	14.87200	6.881	1.7168
P value		0.456		0.511		0.706		0.061

All data are reported as mean ± SD.

ROC curve analysis

The presence of diabetic foot is significantly linked to elevated levels of IL-6, CRP, and HbA1c. The diagnostic accuracy of CRP, IL-6, and HbA1c in predicting diabetic foot was evaluated using the receiver operating characteristic curve. The results indicated that the areas under the curve for CRP, IL-6, and HbA1c were 0.839, 0.728, and 0.834, respectively, indicating a favorable predictive value for each diagnostic marker. The optimal threshold levels for CRP, IL-6, and HbA1c in predicting diabetic foot were determined to be 7.5 ng/ml (with a sensitivity of 82% and specificity of 85%), 22.5 ng/ml (with a sensitivity of 67% and specificity of 58.0%), and 6.15 ng/ml (with a sensitivity of 73% and specificity of 87%), as presented in Table 5 and Fig. 1A. The performance of the stepwise

model was tested after the probability was reduced. ROC curve was done for probability variable saved from the model. The AUC was 0.985 (0.973–0.997) and the P-value <0.001, revealing a very good performance of the stepwise model (Fig. 1B).

Discussion

Peripheral neuropathy, commonly referred to as diabetic foot, is a frequently observed outcome in diabetes mellitus. Diabetic foot ulcers are a leading cause of morbidity and mortality. Lower limb amputation is a consequence of this condition.¹⁰ Timely detection of foot ulcers is crucial for mitigating the likelihood of amputation. We determined the diagnostic significance of proinflammatory

Table 5

Curve analysis of the receiver operating inflammatory markers' characteristics of HbA1c for detection of diabetic foot.

Variables	Cut off point	Sensitivity (%)	Specificity (%)	AUC	P-value
HbA1c	6.15	73	87	0.834 (0.776–0.892)	0.000
TNF	28.5	50	54	0.571 (0.487–0.656)	0.081
IL-6	22.5	67	58	0.728 (0.660–0.796)	0.000
CRP	7.5	82	85	0.839 (0.776–0.901)	0.000

AUC, area under the curve; CRP, C-reactive protein; TNF, tumor necrosis factor; IL-6, interleukin 6; HbA1c, glycated hemoglobin.

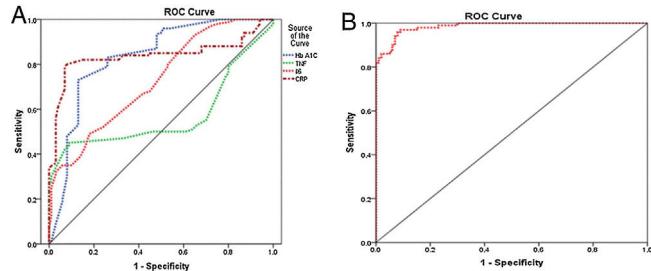


Fig. 1. Receiver operating characteristic curve. (A) Receiver operating characteristic curve shows the specificity and sensitivity of inflammatory markers (CRP, IL-6, and TNF) and HbA1c for diabetic foot prediction. CRP, C-reactive protein; TNF, tumor necrosis factor; IL-6, interleukin 6; HbA1c, glycated hemoglobin. (B) ROC curve for model performance.

markers, namely CRP, IL-6, and HbA1c, in distinguishing diabetic foot from non-diabetic foot. Correlational analyses were performed to investigate the association between the aforementioned biomarkers and multiple factors.

The deleterious effects of diabetes on the kidneys are widely recognized, as they can result in impaired renal function or even renal failure if left unaddressed.¹² The findings of this investigation indicate that, within the population of individuals with diabetic foot, an appreciable increase in the levels of urea and creatinine is a contributing factor to the deterioration of renal function. Furthermore, the outcomes of the regression analysis indicated a link between creatinine levels and the incidence of foot ulcers. Additionally, this study has shed light on the positive correlation between urea concentrations and cytokines such as IL-6 and TNF. The involvement of cytokines in inflammation and subsequent protein catabolism has been found to contribute to elevated urea synthesis, as reported previously.¹³

Dubsky et al. identified poor glycemic control as a contributing factor to diabetic foot.¹⁴ According to a recent study, HbA1c is a significant factor in the development of foot ulcers.¹⁵ Elevated HbA1c levels have the potential to serve as valuable indicators for the onset of peripheral neuropathy. Consequently, enhanced glycemic regulation can facilitate recovery from injury. This assertion is supported by reference.⁹ The findings of our study indicate a statistically significant elevation in HbA1c levels among patients with diabetic foot compared to those with diabetes but without foot complications. A direct association was observed between HbA1c and RBC, whereas an inverse association was noted between HbA1c and MCH. This discovery corresponds to a study conducted by Koga et al.¹⁶ Additionally, a direct association was observed between HbA1c and FBG, which was validated by Khan et al.'s (2016) research.¹⁷ The study conducted by Ketema et al.¹⁸ provided evidence of a positive correlation between HbA1c and the level of blood glucose in the postprandial period, as well as the level of blood glucose in the fasting period. This finding supports the notion that HbA1c levels are positively associated with both FBG and PPBG levels. Moreover, a positive correlation was seen between HbA1c and creatinine levels, which was substantiated by a study conducted by Farasat et al.¹⁹ Unregulated blood glucose levels have a significant effect on the renal system, which may result in gradual deterioration of the glomerular filtration rate

(GFR) and the development of progressive renal ailment.¹² The wound-healing process is significantly affected by pro- and anti-inflammatory cytokines. Any disruption in the immune system can have adverse effects on wound healing, ultimately resulting in diabetic foot disease. This highlights the crucial role of cytokines in the wound-healing process.²⁰ Proinflammatory cytokines, namely TNF- β and IL-6, are significant contributors to the advancement of diabetic foot, as per previous research.⁹ A notable elevation in TNF levels has been observed in individuals with diabetic foot conditions compared to those with diabetes mellitus, but without foot ulcers. El-Sheikh et al. provided support for this finding, as they noticed a higher concentration of TNF in individuals with diabetic foot than in controls.¹⁰ The current study revealed a significant elevation of TNF in diabetic foot ulcerative patients compared with diabetic control patients, but Herder et al. observed that TNF did not exhibit any correlation with diabetic peripheral neuropathy.²¹ This finding contradicts the results of Hussein et al., who reported a positive correlation between elevated TNF levels and diabetic neuropathy severity.²²

The current study revealed a positive correlation between TNF and urea levels, which is consistent with the findings of Ramseyer et al.²³ Their study demonstrated that elevated TNF levels lead to an increase in plasma urea levels. Simultaneously, a negative correlation was observed between TNF and lymphocytes. The aforementioned observation was corroborated by Ulich et al. (1989), who reported the occurrence of TNF-induced lymphopenia.²⁴ Furthermore, a negative correlation was observed between TNF and MCH, consistent with the findings of Kim et al. (2012). According to their study, patients undergoing anti-TNF therapy experience an increase in hemoglobin levels as a result of effective treatment.²⁵

IL-6 is a pro-inflammatory cytokine that augments the likelihood of advancement of foot ulcers.¹⁰ In this study, IL-6 concentrations were observed in the diabetic foot cohort compared to those in the diabetic control cohort. Furthermore, a stepwise logistic regression model confirmed that IL-6 was a significant predictor of diabetic foot in patients with diabetes. This finding is consistent with the research conducted by Zubair et al. (2012), who demonstrated a powerful link between IL-6 and urea. Furthermore, a negative correlation was observed between IL-6 and RBC, as previously reported.⁶ McCranor et al. (2013) provided evidence to support this finding, indicating that the reduction in RBC levels was attributed to inflammation induced by IL-6.²⁶ A weak negative correlation was observed between IL-6 levels and WBC count. It is widely acknowledged that white blood cell (WBCs) levels increase in response to inflammation and specific illnesses.²⁷ This finding contradicts the results of Korkmaz et al. (2018), who reported that increased IL-6 levels are positively associated with elevated WBC counts.²⁸ Furthermore, a robust positive association was detected between the proinflammatory cytokines, TNF and IL-6. Research has demonstrated that diabetic patients exhibit elevated levels of IL-6 and TNF.²⁹

The cytokines IL-6 and TNF are primarily responsible for the release of CRP.³⁰ Elevated CRP levels have been observed in individuals with diabetic foot compared to those in the diabetic control cohort. A previous investigation established a correlation between elevated CRP levels and the onset of diabetic foot, as evidenced by reference.³¹ The results of our stepwise logistic regression analysis

indicated that CRP level is a predictor of the development of diabetic foot. Furthermore, a direct association was observed between CRP levels and LDL, TG, and cholesterol levels. Dongway et al. (2015) provided evidence to support this finding and demonstrated a positive correlation between CRP and LDL levels.³⁰ The present author concurs with Kumira et al.'s (2021) findings, which indicate a positive association between CRP and LDL, as well as total cholesterol.³² Zubair et al. (2012) reported a correlation between triglyceride (TG) levels. A positive correlation was observed between CRP levels and mean corporcular volume. Furthermore, a direct relationship exists between HbA1c and CRP. This, which is supported by Seo et al. (2021), who reported a strong positive correlation between high CRP levels and poor blood glucose control.³³ In contrast, Bahrami et al. (2007) reported no significant correlation between HbA1c and CRP, as stated in reference.³⁴

Receiver operating characteristic (ROC) curves were utilized to investigate the association between the progression of diabetic foot and the biomarkers IL-6, CRP, and HbA1c. The results indicated that CRP exhibited superior specificity and sensitivity compared to the other markers. The results of this investigation demonstrated that CRP, IL-6, and HbA1c possess significant diagnostic utility as markers, exhibiting superior AUC, sensitivity, and specificity in distinguishing diabetic foot ulcers from non-diabetic foot ulcers. According to previous research, optimal specificity and sensitivity can be achieved by utilizing a minimum of three markers in combination.²⁸ The optimal threshold levels for CRP, IL-6, and HbA1c in the diagnosis of diabetic foot ulcers were 7.5, 22.5, and 6.15 ng/ml, respectively. The confirmed role of CRP, IL-6, and HbA1c as markers for diabetic foot progression allows their utilization in a scoring system designed to assess the severity of foot ulcers.

Limitations

The small sample size and unknown duration of ulcers and infections are among the limitations of the present study.

Conclusion

Our results validated the significance of IL-6, CRP, TNF, and HbA1c as potential biomarkers for the diagnosis and prediction of diabetic foot. Furthermore, a positive correlation was observed between TNF and CRP levels. In addition, a significant association was observed between CRP and HbA1c, indicating a positive correlation between the two variables. The study findings indicated that IL-6, CRP, and HbA1c were the most significant factors that facilitated the progression of foot ulcers. However, TNF was not a distinguishing factor between diabetic and non-diabetic foot patients. The utilization of a combination of these biomarkers has the potential to effectively manage the likelihood of lower-limb amputation. This method is considered a straightforward and efficient approach for identifying patients with diabetes who are at a high risk of developing diabetic foot.

Ethical considerations

This study was performed in accordance with the ethics guidelines and approved by the ethics committee of Affiliated GOTHI (ethic approval No: IDE00290).

Informed consent

Written informed consent was obtained from all study participants.

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Qatar library will cover the cost of open access publication of this study.

Conflict of interest

Authors declare no conflict of interest.

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