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Inflammatory Markers and Diabetic Foot: Their Role in Type 2 Diabetes Patients at H. Adam Malik Hospital

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ABSTRACT

Introduction. Diabetic foot is a severe complication of type 2 diabetes mellitus, resulting from chronic hyperglycemia, vascular disorders, neuropathy, and infection. Inflammatory markers such as C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), fibrinogen, and D-dimer reflect inflammation and coagulation that worsen diabetic foot conditions. However, data from the local population in Medan remain limited. **Methods.** This cross-sectional study was conducted at H. Adam Malik General Hospital, Medan, from May to June 2025. Participants were hospitalized patients with type 2 diabetes mellitus, both with and without diabetic foot, recruited by consecutive sampling. Inclusion criteria were patients ≥18 years with type 2 diabetes, with or without diabetic foot (grade II–V). Exclusion criteria included chronic diseases (HIV, malignancy, autoimmune), concurrent infections, use of anticoagulants, NSAIDs, steroids, hormones, immunomodulators, pregnancy, or incomplete records. Data on demographics, HbA1c, CRP, ESR, fibrinogen, and D-dimer were analyzed with significance set at $p<0.05$. **Results.** A total of 63 patients were included. BMI showed a significant association with diabetic foot ($p<0.05$), while age, sex, and HbA1c did not. Levels of CRP, ESR, fibrinogen, and D-dimer were significantly higher in patients with diabetic foot than those without ($p=0.001$). CRP was also significantly associated with ulcer severity based on Wagner classification. **Conclusion.** CRP, ESR, fibrinogen, and D-dimer were elevated in diabetic foot patients, with CRP as the strongest predictor of ulcer severity. Monitoring these markers is essential for risk assessment and management of diabetic foot in type 2 diabetes.

1. Introduction

Peripheral Artery Disease (PAD) in type 2 diabetes mellitus (T2DM) can lead to diabetic foot, one of the most serious and long-term complications of diabetes, imposing a significant social burden in terms of amputations and reduced quality of life. The prevalence of diabetic foot among individuals with diabetes ranges from 15% to 25%. However, epidemiological data on diabetic foot, particularly in the city of Medan, remain very limited in publicly available sources. The recurrence rates within the first five years being extremely high between 50% and 70% and is associated with hyperglycemic emergencies and increased hospitalizations.[1] Chronic hyperglycemia in T2DM triggers peripheral vascular changes that result in endothelial dysfunction, reduced vasodilator production, and ischemia. Along with neuroarthropathy and immune dysfunction, these factors contribute to the pathophysiology of diabetic foot.[1,2]

As an inflammatory biomarker, C-Reactive Protein (CRP) increases sharply in response to infection or tissue damage, including in cases of diabetic foot. Several studies have demonstrated a significant association between elevated CRP levels and the risk and severity of diabetic foot. A study by Weigelt et al. found that the severity of diabetic foot strongly correlated with elevated levels of CRP, fibrinogen, and IL-6.[3] A meta-analysis by Zhang et al. also highlighted a strong link between CRP levels and diabetic foot infections, showing higher CRP levels in diabetic ulcer patients compared to controls.[4] Furthermore, a study by Asten et al. stated that CRP levels could be used as a predictive factor to monitor treatment success in

diabetic foot disease with osteomyelitis.[5]

Recent studies have shown that Erythrocyte Sedimentation Rate (ESR) and CRP can serve as diagnostic predictors of osteomyelitis in diabetic foot. ESR is an acute-phase inflammatory marker that reflects erythrocyte aggregation due to increased plasma proteins such as fibrinogen and immunoglobulins. An ESR value >70 mm/h, especially when accompanied by CRP >7.9 mg/L, is often associated with a high likelihood of osteomyelitis.[6,7] ESR may also serve as a predictive parameter for lower limb amputation.[8] A study by Yapici et al. reported a mean ESR value of 89 mm/h, with higher ESR levels observed in patients with osteomyelitis compared to those without osteomyelitis.[9]

Fibrinogen is an acute-phase protein that functions as a marker of systemic inflammation and is associated with coronary and vascular disease risk. Increased fibrinogen levels result from adipose tissue expansion, leading to hypoxia, cell death, and the release of proinflammatory cytokines.[10] Weigelt et al. found that levels of acute-phase proteins like fibrinogen increased significantly about 1.4 times the normal value in patients with diabetic foot. Furthermore, elevated fibrinogen levels were significantly associated with ulcer severity and the degree of infection in patients.[11]

D-dimer is a fibrin degradation product that reflects a hypercoagulable state and acts as an acute-phase reactant capable of triggering an inflammatory response through neutrophil and monocyte activation and IL-6 release. D-dimer levels often increase in vascular disorders and angiopathic complications of diabetes, including peripheral neuropathy. A study by Zhuang et al. showed that elevated D-dimer levels were significantly associated with the occurrence of peripheral neuropathy in T2DM, which is caused by microvascular impairment, endothelial dysfunction, and endoneural hypoxia due to insufficient neural blood flow. Zhang et al. also found that mean D-dimer levels were higher in patients who underwent amputation compared to those who did not.[12,13]

Previous studies have demonstrated that CRP[3,14,15,16,17], ESR[3,5,18], Fibrinogen[3,19,20] and D-dimer[12,21,22] can serve as inflammatory markers associated with T2DM, particularly in relation to diabetic foot.[3,23] However, to date, no studies have investigated the role of inflammatory markers in the incidence of diabetic foot among the diabetic population in Medan.

2. Methods

This study is an analytical observational research conducted using a cross-sectional design. It was carried out in the Inpatient Ward of Adam Malik General Hospital in Medan, Indonesia, using medical record data collected from May to June 2025. The study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara, with ethical clearance number 201/KEPK/USU/2025.

The inclusion criteria were patients aged over 18 years, either newly or previously diagnosed with type 2 diabetes mellitus, with or without diabetic foot complications (grade II–V), who were hospitalized at Adam Malik General Hospital. Exclusion criteria included patients with other chronic diseases such as HIV, malignancy, autoimmune disorders, or other infections; patients taking anticoagulants, NSAIDs, steroids, hormonal therapy, or immunomodulators; pregnant women; and patients with incomplete medical records. The minimum required sample size was 31 subjects per group, and the sampling method used was consecutive sampling.

All research subjects who met the inclusion and exclusion criteria were categorized into two groups: those with diabetic foot and those without. Data on baseline characteristics (such as age, sex, BMI, and HbA1c) were collected to describe the demographic profile, along with laboratory results including CRP, ESR, fibrinogen, and D-dimer as inflammatory markers. All data were collected and analyzed statistically.

Data were analyzed descriptively to examine the frequency distribution of research subjects based on sample characteristics. Prior to bivariate analysis, a normality test was performed. Statistical analysis was conducted using IBM SPSS Statistics software version 25.

The comparison of demographic characteristics between the two groups (diabetic foot group and diabetic control group) was conducted according to the type and distribution of each variable. For categorical data, if the distribution was normal ($p > 0.05$), the chi-square test was used; if not ($p < 0.05$), Fisher's exact test was applied. For numerical data with two groups, the independent t-test was used if the data were normally distributed ($p > 0.05$); otherwise, the Mann–Whitney test was used ($p < 0.05$). For numerical data with more than two groups, one-way ANOVA was used if the data were normally distributed, and the Kruskal–Wallis test was used if the data were not normally distributed. Results were considered statistically significant at $p < 0.05$ with a 95% confidence level.

3. Results

In total, the study included 32 patients with diabetic foot and 31 patients without diabetic foot, all diagnosed with type 2 diabetes mellitus. The subject characteristics were showed in Table 1.

Table 1. Study characteristics

Variable	Diabetic foot		*p*
	Present	Absent	
Age (years)	57.7 ± 8.4	59.2 ± 12.4	0.581[a]
Body Mass Index (kg/m^2)	23.8 (17.3 – 30.9)	22.0 (15.6 – 29.3)	0.005[a]*
Gender, n (%)			0.287[b]
Female	8 (12.7)	12 (19.0)	
Male	24 (38.1)	19 (30.2)	
HbA1c (%)	9.59 ± 2.77	0.198	0.557[a]

[a]Independent T test, p = 0.05
[b]Chi-Square test, p = 0.05

Table 2. Association between inflammatory markers and the incidence of diabetic foot in patients with type 2 diabetes mellitus

Variable	Diabetic foot		*p*
	Present	Absent	
CRP (mg/L)	1.4 (0.7 – 12.0)	0.3 (0.1 – 0.6)	0.001[a]*
ESR (mm/jam)	110.0 (30.0 – 153.0)	20.0 (8.0 – 91.0)	0.001[a]*
Fibrinogen (mg/dl)	680.0 (370.0 – 910.0)	300.0 (104.0- – 1322.0)	0.001[a]*
D-dimer (ng/mL)	1975.0 (790.0 – 14,060.0)	550.0 (190.0 – 9070.0)	0.001[a]*

[a]Mann Whitney test, p = 0.05

Table 3. Association between inflammatory markers and diabetic foot severity in patients with type 2 diabetes mellitus

Variable	Diabetic foot				*p*
	Wagner II	Wagner III	Wagner IV	Wagner V	
CRP (mg/L)	1.4 (0.7 – 1.4)	1.4 (1.4 – 2.0)	1.4 (1.4 – 12.)	2.8 (0.7 – 3.0)	0.030[b*]
ESR (mm/jam)	90.0 (31.0 – 110.0)	90.0 (30.0 – 153.0)	126.0 (63.0 – 139.0)	110.0 (65.0 – 131.0)	0.116[b]
Fibrinogen (mg/dl)	550 (500.0 – 740.0)	660.0 (417.0 – 880.0)	680.0 (467.0 – 880.0)	680.0 (370.0 – 910.0)	0.697[a]
D-dimer (ng/mL)	550.0 (190.0 – 9070.0)	1500.0 (930.0 – 3720.0)	1650.0 (870.0 – 7800.0)	1810.0 (1000.0 – 4100.0)	0.259[b]

[a]One Way Annova test, p = 0.05
[a]Kruskal Wallis test, p = 0.05

Among the 63 subjects with type 2 diabetes mellitus, a higher BMI (median 23.8) was significantly associated with the occurrence of diabetic foot (p = 0.005). In contrast, age and sex showed no significant associations (p = 0.581 and p = 0.277, respectively). The majority of subjects were male (69.3%). The mean HbA1c level was higher in patients with diabetic foot (9.59 ± 2.77) compared to those without (9.45 ± 3.13), although the difference was not statistically significant (p = 0.557). The relationship between inflammatory markers and the incidence of diabetic foot in patients with type 2 diabetes mellitus is presented in Table 2.

The analysis showed that all inflammatory markers (CRP, ESR, fibrinogen, and D-dimer) were significantly higher in patients with diabetic foot compared to those without (all p = 0.001). The median levels of CRP, ESR, fibrinogen, and D-dimer in patients with diabetic foot were 1.4 mg/L, 110 mm/h, 680 mg/dL, and 1,975 ng/mL, respectively. These findings indicate a strong association between elevated inflammatory markers and the incidence of diabetic foot in patients with type 2 diabetes mellitus. The association between inflammatory markers and diabetic foot severity in patients with type 2 diabetes mellitus were showed in Table 3.

This study found that among all the inflammatory markers analyzed, only CRP showed a statistically significant association with the severity of diabetic foot based on the Wagner classification (p = 0.030). The median CRP level increased with the degree of severity, reaching the highest value at grade V (2.8 mg/L). Meanwhile, although ESR, fibrinogen, and D-dimer levels tended to increase, their associations were not statistically significant (p = 0.116, 0.697, and 0.259, respectively). These findings highlight CRP as the most relevant inflammatory marker in reflecting the severity of diabetic foot.

4. Discussion

This study found that the incidence of diabetic foot among patients with type 2 diabetes mellitus was more common in the younger age group, although the difference was not statistically significant (p = 0.581).

This finding differs from the study by Zhu et al., which reported that diabetic foot occurred more frequently in older individuals. In addition, although males made up the majority of the patient population, sex was also not significantly associated with the incidence of diabetic foot (p = 0.277). These results are consistent with the studies by Notu et al., Lu et al., and Li et al., which also showed male predominance among diabetic foot cases.[24,25,26] This study showed that patients with a higher body mass index (BMI) had a statistically significant association with diabetic foot occurrence in type 2 diabetes patients. This finding aligns with the study by Zhu et al., which also found a higher BMI in patients with diabetic foot. Most patients in this study had moderate to severe ulcers (grades III–V), with the most common location being the plantar surface.[27] However, this result contrasts with the study by Li et al., which found a higher BMI in patients without diabetic foot.[25]

Higher HbA1c levels were observed in patients with diabetic foot compared to those without, although the difference was not statistically significant (p = 0.557). This is consistent with the study by Li et al., which reported a similar trend. HbA1c reflects long-term glycemic control, and elevated levels indicate chronic hyperglycemia, which can lead to vascular damage, oxidative stress, and inflammatory activation, thereby impairing wound healing and worsening diabetic foot conditions.[3]

This study showed that inflammatory markers such as CRP, ESR, fibrinogen, and D-dimer were significantly higher in patients with diabetic foot compared to those without (p = 0.001). These findings are consistent with the study by Li et al., which also reported elevated fibrinogen levels in diabetic foot patients. CRP and fibrinogen levels were also notably higher in patients with more severe diabetic foot grades (grades III–V), showing strong and significant correlations. The study established cut-off values for fibrinogen at 513 mg/dL (sensitivity: 80.9%; specificity: 82.6%) and CRP at 28.18 mg/L (sensitivity: 73.7%; specificity: 89.1%), indicating that both markers are fairly sensitive and specific in predicting diabetic foot occurrence in type 2 diabetes patients.[25] Another study by Khan et al. also found an association between plasma fibrinogen levels and BMI, ulcer depth, and an ABI score < 0.4.[28] Hadavand et al. found that procalcitonin (PCT), CRP, and ESR levels were significantly higher in patients with grade 4 diabetic foot compared to those with grade 3, with all three markers showing statistically significant differences. That study also included an analysis of the cut-off values, sensitivities, and specificities of each inflammatory marker in predicting ulcer severity. The identified cut-off values for PCT, CRP, and ESR were 0.35 (sensitivity: 74.54%; specificity: 55.65%), 44.0 (sensitivity: 65.57%; specificity: 46.78%), and 61.5 (sensitivity: 63.68%; specificity: 52.28%), respectively.[18] Mohamed et al. also analyzed differences in HbA1c, CRP, and other inflammatory markers such as leukocyte count, lymphocyte count, TNF, and IL-6 between diabetic foot and non-diabetic foot populations. That study found significant differences in all the above markers between the two groups. Furthermore, the reported cut-off values with corresponding sensitivities and specificities were 7.5 for CRP (sensitivity: 82%; specificity: 85%) and 6.15 for HbA1c (sensitivity: 73%; specificity: 87%). These two markers had higher sensitivity and specificity compared to TNF and IL-6 in that study.[3] Zhuang et al. demonstrated that D-dimer levels were significantly associated with the occurrence of peripheral neuropathy in diabetes. This is likely due to the progression of diabetes and its complications, including increased neural latent action potential and reduced nerve response in type 2 diabetes. Elevated D-dimer can lead to a hypercoagulable state, which may contribute to microvascular disease and endothelial dysfunction, resulting in impaired neural blood flow, endoneural hypoxia, and neuronal damage.[12]

Overall, CRP, ESR, fibrinogen, and D-dimer reflect inflammatory and coagulation processes that exacerbate the course of diabetic foot. Therefore, monitoring these biomarkers is essential for assessing ulcer severity, risk of complications, and response to therapy in patients with diabetic foot. The main strength of this study is its novelty in simultaneously evaluating the association between inflammatory markers and diabetic foot in type 2 diabetes patients within the Indonesian population. The limitation of this study lies in its cross-sectional design, in which all variables were assessed simultaneously at a single point in time without controlling for potential confounding variables. Future studies are recommended to employ a prospective cohort or longitudinal design to better establish causal relationships between inflammatory markers and the development or progression of diabetic foot in patients with type 2 diabetes mellitus. In addition, future research should include a larger and more diverse population across multiple healthcare centers to improve the generalizability of the findings.

5. Conclusion

This study demonstrated that inflammatory markers CRP, ESR, fibrinogen, and D-dimer were elevated in patients with diabetic foot, with CRP being the most significant indicator of wound severity. CRP and fibrinogen also showed good sensitivity and specificity in predicting the occurrence of diabetic foot.

6. Author Contribution

S.F.S. , Z.Z and S.S. carried out the experiment. S.F.S wrote the manuscript with support from Z.Z and S.S. Z.Z and S.F.S conceived the original idea and S.S. supervised the statistical analyses.

7. Acknowledgements

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