Molecular Signals in Diabetic Foot Ulcers: Signature markers across different grades of DFU

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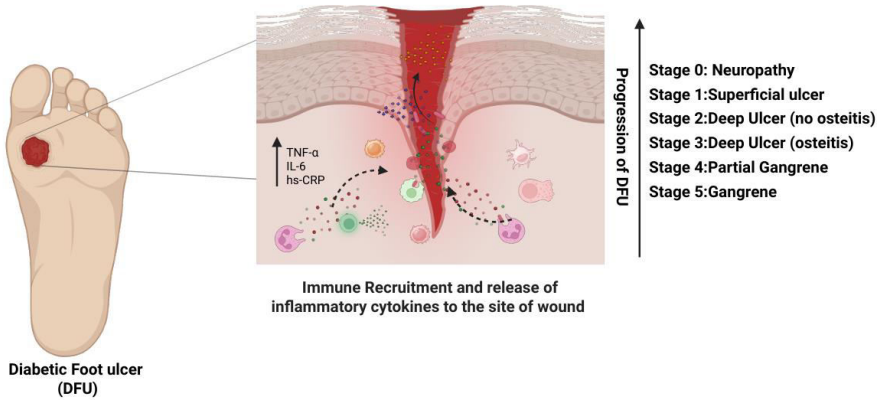
ABSTRACT

Graphical Abstract



Highlights

- DFU needs early care ; inflammation markers guide targeted treatment.
- Strong correlation links inflammation and ulcer progression.
- Inflammatory markers TNF-α, IL-6, and hs-CRP are elevated in DFU patients and increase progressively with ulcer severity.
- The study demonstrates that inflammatory marker levels correspond with Wagner grades of diabetic foot ulcers.
- Biomarkers TNF-α, IL-6, and hs-CRP enable early detection and guide targeted DFU therapy.

Abstract

Introduction: Diabetic foot ulcers (DFUs) represent a major complication of diabetes mellitus, characterized by heightened morbidity and amputation risk. Elucidating the molecular drivers of inflammation across DFU grades is vital for informed diagnosis, stratified care, and optimized therapeutic intervention.

Aim : This study aimed to determine the serum levels of Tumour necrosis factor-α (TNF-α), Interleukin 6 (IL-6), and high Sensitivity C-Reactive Protein (hs-CRP) levels and in DFU and Diabetes patients without foot ulcer, and to correlate them with severity in different grades of DFU.

Methods: A total of 250 subjects were enrolled, including 125 diabetic patients with foot ulcers and 125 without. Relevant clinical parameters and comorbidities were retrieved from the electronic medical repository. Serum levels of TNF-α, IL-6, and hs-CRP were quantified using ELISA method.

Result: Serum levels of TNF-α, IL-6, and hs-CRP were significantly higher in diabetic patients with foot ulcers compared to diabetic patients without ulcers ($P < 0.001$). Furthermore, these inflammatory markers showed a progressive increase with higher Wagner grades of DFUs. A strong positive correlation was observed between the severity of the ulcer (as per Wagner classification) and the levels of TNF-α, IL-6, and hs-CRP ($P = 0.001$), indicating that inflammation intensifies with ulcer progression.

Conclusion: Elevated levels of TNF-α, IL-6, and hs-CRP levels in DFU patients correlate with ulcer severity, highlighting their prognostic potential. These markers may support earlier detection and targeted therapeutic strategies.

KEYWORDS: Diabetic foot ulcers, Wagner classification, IL-6, TNF-α, hs-CRP, ELISA

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INTRODUCTION

Diabetic foot ulcer (DFU), particularly when complicated by infection remains a significant cause of morbidity among individuals with diabetes leading to dreaded complications like gangrene and amputations. It is estimated that 15–25% of diabetic patients will develop a chronic foot ulcer during their lifetime [1, 2]. Despite global advancements in preventive strategies and wound care, DFUs continue to account for a large proportion of lower limb amputations [3]. The primary risk factors for foot ulcers are diabetic neuropathy and peripheral arterial disease. Diabetic Foot ulcer is increasingly recognized not only as a metabolic disorder but also as a state of chronic low-grade inflammation. A complex interplay exists between inflammatory mediators and metabolic dysfunction, contributing significantly to cardiovascular risk. Emerging evidence suggests that hormones, cytokines, and various inflammatory markers interact in a dynamic network, further complicating disease progression and systemic effects [4, 5].

Despite increasing recognition of inflammation in metabolic diseases, data specifically addressing the role of systemic inflammation in diabetic foot ulcers (DFUs) remain limited. Chronic low-grade immune activation is a known risk factor for the development of type 2 diabetes [6], and it is also implicated in both macrovascular complications such as myocardial infarction and stroke, and microvascular complications like neuropathy and nephropathy [7]. Key inflammatory markers including interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), and tumor necrosis factor-alpha (TNF-α) have shown associations with insulin resistance and obesity [8].

The immune system plays a pivotal role at multiple stages in the development and progression of chronic wounds. Similar to its involvement in the early stages of type- 2 diabetes and cardiovascular disease, immune activation may also precede the onset of DFUs. Pro- inflammatory pathways are integral to the wound healing process; any dysregulation in immune function may disrupt tissue repair and homeostasis. This can contribute to the persistence of non-healing, chronic wounds that characterize diabetic foot syndrome. (6) Because of the limited treatment availability and serious consequences, diabetic foot syndrome is becoming an important issue. An inflammatory cascade through increased expression of proinflammatory cytokines exist in diabetic foot, whereas no study, to our knowledge, evaluated the role of TNF-α, IL- 6 and Hs-CRP and immune-inflammatory biomarkers such as inflammatory cytokines in patients with different grades of DFU .

Based on this rationale, our study aimed to evaluate the circulating levels of IL-6, hs-CRP, and TNF-α in individual with diabetic foot ulcers compared to diabetic patients without foot complications in different stages which may help in better understanding the pathogenesis of DFU and correlate the values with its severity.

METHODS

Study population

A total of 125 diabetic foot ulcer patients (25 patients in each stage of DFU) and 125 diabetic patients without foot ulcer (free from foot wounds and acute or chronic disease(DWO), admitted to surgery wards was enrolled in the study. Multiple classification systems exist for diabetic foot ulceration and foot syndrome. The most widely recognized classification is the Wagner system, which grades ulcers from 0 to 5 based largely on ulcer depth and Severity (9).All wounds were graded when they got admitted to the hospital according to the Wagner classification system into five grades (grade I - grade V), the number of patients in each group was 25.Foot ulcer was defined as a full-thickness skin defect that required ≥14 days for healing. DFU and DWO will be matched for age and sex. Patients with inflammatory or infectious diseases, autoimmune and rheumatic diseases, cancer, hematological diseases, malignancy, Pregnancy ,lactation ,Chronic inflammatory disorders, severe renal or liver failure, recent venous thromboembolism ,as well as those who were under treatment with immunodeficiency drugs , was excluded from study .

Clinical sampling procedure

Using aseptic precautions 5 ml of venous blood with and without anticoagulant was collected from the patients and controls after obtaining due consent and clearance from the Institutional Ethical Committee before the commencement of the study. All the blood samples were stored for 30 min at room temperature in the vacutainer, Coagulate at room temperature for 10-20 minutes;

centrifuge for 20-min at 2000-3000 rpm and supernatant was removed. If precipitation appears, recentrifuge, and the supernatants were aliquoted and stored at -80°C until further analyses.

ELISA-based estimation of inflammatory biomarkers

Serum IL-6, hs-CRP and TNF-α level of all samples were measured using a GENLISA™ ELISA kit from Krishgen Biosystems, USA. Assays employ a quantitative sandwich ELISA technique. The color intensity in each well will be measured at 450 nm for Serum IL-6, hs-CRP and TNF-α, using an automated iMark ELISA reader from Biorad laboratories. The detectable concentrations ranged from 7.8pg/ml to 500pg/ml for TNF, 6.25pg/ml to 400pg/ml for IL-6, and for hs- CRP found to be less than 0.112 µg/ml as quoted by the manufacturer.

Statistical Analysis

Data was coded in MS Excel and all statistical analysis was carried out using R software (V 4.5.1). The data was checked for Normal distribution using the Shapiro- Wilk test. The significant difference between two groups (DFU and DWO) of continuous variables was assessed through Student t or Welch t or Mann-Whitney U as applicable. The summary of categorical variables will be reported in terms of frequencies and percentage.The association between the categories will be assessed using Chi-square test or Fisher's exact test.It is observed that all the variables do not follow Normality. Thus the statistical difference between the six groups was assessed through Kruskal Walli's test. If null hypothesis is rejected, then post-hoc test (with Bonferroni correction) was carried out for pair-wise comparisons. A p value < 0.05 was considered statistically significant.

Ethics

The study is registered in the Clinical Trials Registry- India with reference no CTRI/2023/07/055588.Also, was approved by the Research Ethics Committee of the Yenepoya (Deemed to be University) (reference number- YEC-1/2023/172) and all subjects gave written informed consent.

RESULTS

A total of 125 DFU patients and 125 DWO patients, admitted to surgery wards from Yenepoya Medical College, Mangalore were selected. Age and sex were matched between the two groups. The subjects' ages ranged from 34 to 60 years. Among DFU patients, 25 individuals were enrolled for each Wagner stage (grades 1 to 5) to ensure balanced representation across the spectrum of ulcer severity. The baseline demographic and clinical characteristics are detailed in Table 1.The mean age was similar between DFU (57.30 ± 11.01 years) and DWO (57.17 ± 10.47 years) groups ($p = 0.965$), with both groups having the same male-to-female ratio (80% male, 20% female).The duration of diabetes was significantly longer in DFU patients (117.81 ± 89.34 months) compared to DWO (125.28 ± 69.43 months), ($p < 0.001$).A significantly higher number of DFU patients had a history of smoking, alcohol consumption, insulin usage, and hypertension. A positive family history of diabetes was significantly more prevalent in the DWO ($p < 0.001$), suggesting genetic factors alone may not predict DFU development. DFU patients had higher mean HbA1c levels ($9.49 \pm 2.50\%$) compared to DWO ($8.63 \pm 2.52\%$) ($p = 0.007$), indicating poorer glycemic control. Inflammatory markers: DFU patients had a significantly higher ESR (64.02 ± 26.56 mm/hr) than DWO (48.7 ± 27.1 mm/hr) ($p < 0.001$).Lipid profile: Total cholesterol (TC) and LDL levels were lower in DFU patients ($p < 0.001$), while HDL was slightly higher. Triglyceride levels were significantly lower in DFU patients ($p = 0.036$).Renal markers: Serum urea and creatinine were significantly elevated in the DWO group, possibly due to associated renal complications ($p = 0.039$ and $p = 0.015$, respectively) as shown in Table 2. Table 3 shows a progressive increase in inflammatory markers was observed across DFU grades: IL-6 rose from 0.05 ± 0.00 pg/mL in Grade 1 to 2.66 ± 0.39 pg/mL in Grade 5. hs-CRP increased from 0.14 ± 0.04 µg/mL (Grade 1) to 0.68 ± 0.24 µg/mL (Grade 5).TNF-α increased from 2.24 ± 0.21 pg/mL in Grade 1 to 4.92 ± 0.80 pg/mL in Grade 5.Compared to DWO, who had significantly lower values (IL-6: 0.06 ± 0.01 pg/mL, hs-CRP: 0.15 ± 0.03 µg/mL, TNF-α: 2.22 ± 0.14 pg/mL), DFU patients showed statistically significant elevations in all three markers ($p < 0.001$).The correlation between inflammatory marker levels and Wagner grades was strong and statistically significant ($P = 0.001$), indicating increasing systemic inflammation with ulcer severity.Figure 1 illustrates representative clinical images of DFUs across different Wagner grades, demonstrating the progression from mild to severe ulceration. Figure 2 presents stage-wise comparisons of serum ,Interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), and Tumor Necrosis Factor-alpha (TNF-α) levels between DFU and DWO. The results showed that serum levels of TNF-α, IL-6, and hs-CRP were significantly elevated in DFU patients compared to DWO ($P < 0.001$).

Table 1: Demographic and baseline data of the Subjects

Variables	DFU	DWO	p value
Age	57.30±11.01	57.17±10.47	0.965[b]
Sex n (%) Male/Female	100/25(80.0%/20.0)	100(80.0%/20.0%)	1.00[a]
Duration of DM(months)	117.81±89.34	125.28±69.43	<0.001***[b]
Smoking History			
Current	7(5.6%)	35(28.0%)	<0.001***[a]
Never	71(56.8%)	43(34.4%)	
Past	47(37.6%)	47(37.6%)	
Alcohol History			
Current	10(8.0%)	31(24.8%)	0.0008***[a]
Never	76(60.8%)	55 (44.0%)	

Past Drug History	39(31.2%)	39(31.25%)	
Insulin	63(50.4%)	32(25.6%)	<0.001***[a]
Tablet	17(13.6%)	68(54.4%)	
Insulin & tablet	45(36.0%)	25(20%)	
History of Hypertension Yes/No	89/36(71.2%/28.8%)	63/40(61.2%/38.8%)	<0.001***[a]
Family history of diabetes Yes/No	28/77(38.4%/61.6%)	97/28(77.6%/22.45)	<0.001***[a]

[a] Chi-square test was performed and [b]Mann-Whitney U test

Table 1. Data represented as mean ± SD; n = number of subjects. Gender and other variables are expressed as frequency with percentage in parenthesis. [a] Chi-square test was performed and [b]Mann-Whitney U test was performed .Abbreviations used: DFU: Diabetic foot ulcer, DWO: Diabetic patient without foot ulcer. Level of significance: * p<0.05,***p<0.001 p>0.05 non significant (ns).

Table 2: Comparison of Clinical and Biochemical Parameters between DFU and DWO

Variable	DFU	DWO	p value
Duration of DM(months)	117.81±89.34	125.28±69.43	<0.001[b]
FBS	159.86±43.41	154.85±36.74	0.325[a]
PPBS	244.97±64.15	249.27±57.95	0.578[a]
HbA1c (%)	9.49±2.50	8.63±2.52	0.007[a]
ESR(mm/1hr)	64.02±26.56	48.7±27.1	< 0.001[a]
TC	181.87±49.26	208.95±54.24	<0 .001[a]
TG	174.92±54.74	188.61±47.67	0.036[a]
LDL	116.19±26.12	129.31±36.02	<0.001[c]
HDL	40.66±37.12	33.19±6.96	0.028[a]
Urea(mg/dL)	32.88±28.32	40.22±27.68	0.039[a]
Creatinine(mg/dL)	1.20±1.37	1.81±2.41	0.015[b]

[a]independent t test [b] Welch t test [c]Mann Whitney U test

Table 2. Data represented as mean ± SD; n = number of subjects. Gender is expressed as frequency in parenthesis. [a]independent t test [b] Welch t test [c]Mann Whitney U test was performed Abbreviations used: DFU:Diabetic foot ulcer, DWO: Diabetic patient without foot ulcer. Level of significance: Level of significance: * p<0.05,*p<0.001 p>0.05 non significant (ns).**

Table 3: The Wagner-ulcer classification system with 5 different DFU grades

DFU Grades	Symptoms	IL-6 pg/mL	hs-CRP µg/mL	TNF-α pg/mL
Controls	Diabetes patients without foot ulcer	0.06±0.01	0.15±0.03	2.22±0.14
1	No ulcer High-risk foot	0.05 ± 0.00	0.14 ± 0.04	2.24 ± 0.21
2	More deep ulcers, with soft tissue infections deep abscess	0.32 ± 0.47	0.29 ± 0.17	2.17 ± 0.13
3	Deep ulcer, abscess with osteomyelitis	0.91 ± 0.59	0.35 ± 0.13	3.90 ± 1.13

4	Localised gangrene, ischemic gangrene	1.64 ± 0.64	0.45 ± 0.21	4.70 ± 0.64
5	All gangrene	2.66 ± 0.39	0.68 ± 0.24	4.92 ± 0.80

Table 3. Data represented as mean ± SD

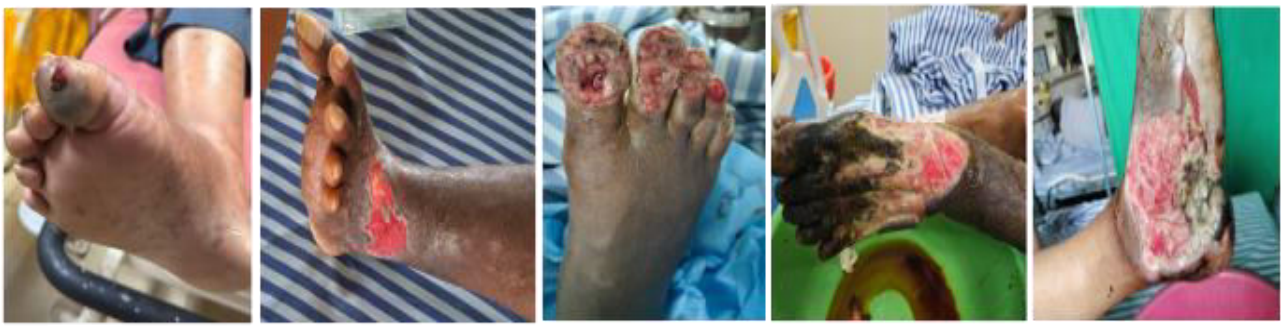

Figure 1. Representative images showing different grades of diabetic foot ulcers. The images illustrate the progression of diabetic foot ulcers from mild to severe stages. (A) Grade 1: Early-stage ulcer with localized tissue damage and minor infection.(B) Grade 2: Moderate ulcer with deeper tissue involvement and visible wound expansion.(C)Grade 3: Severe ulcer with extensive tissue necrosis exposed underlying structures, and infection. (D) Grade 4: Advanced stage characterized by widespread gangrene and tissue destruction.(E) Grade 5: Extensive ulceration with significant necrosis and risk of limb loss.

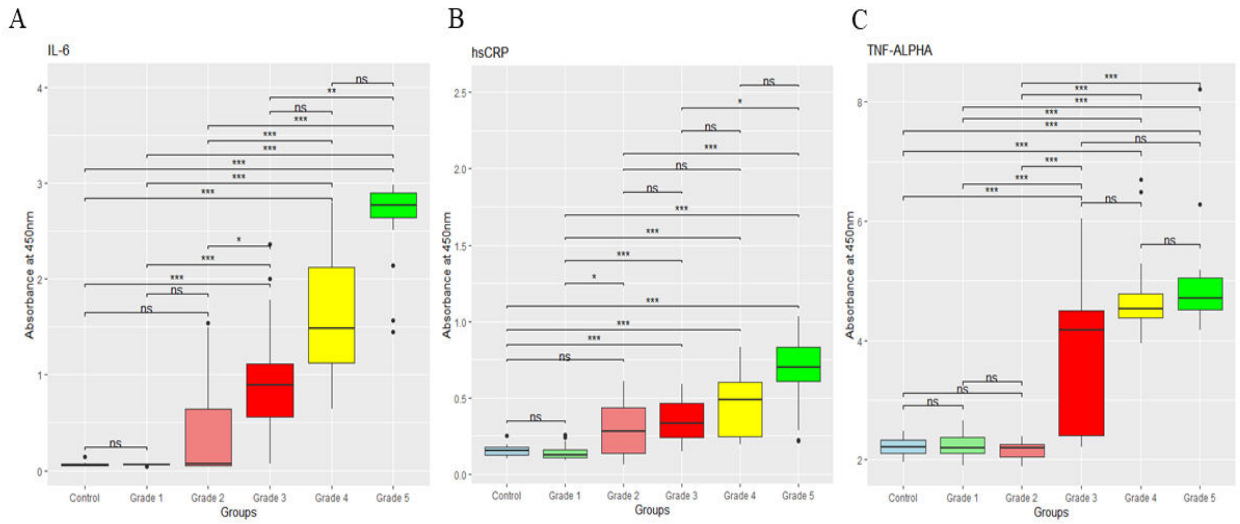

Figure 2. Stages comparisons of levels of Serum IL-6, hs- CRP, and TNF-α in cases and controls. A) IL-6 B) hs- CRP C) TNF-α. ***p value is obtained from post-hoc test with Bonferroni correction. Level of significance: * p<0.05 significant, p>0.05 non significant (NS), ***p<0.001 .***

DISCUSSION

Infected DFU is a common cause of morbidity, ultimately leading to dreaded complications like gangrene and amputations (10). Inflammation is a key component in the pathogenesis of DFUs, and various inflammatory markers such as IL-6, hs-CRP and TNF-α, have been implicated in the development and progression of these ulcers (11).

Diabetic foot wounds are marked by a persistent and dysregulated inflammatory phase, an enhanced production and release of proinflammatory cytokines causes disturbance the balance between proinflammatory and anti-inflammatory macrophages(12). Cytokines are small proteins, soluble in the serum and interacting with cell surface receptors. They serve as a communication network between cells. By interaction with specific transmembrane receptor, they activate signal cascade, which result in cellular response (13). These cytokines may mediate the synthesis of acute phase proteins which are able to initiate and support inflammatory process in the vascular wall(14). Interleukins (ILs), produced by blood monocytes and tissue macrophages, are a group of cytokines that are critical important for the function of the immune system – both innate and adaptive. When the body is infected, ILs is secreted onto target cells and bind to the signals on the surface that activate the target cells, altering cell behavior. ILs levels would be elevated in patients with DFU along with the development of insulin resistance, abnormal healing and

decreased with the healing of ulcers (15).

Similar to the literature, in this study we found that DFW had significantly elevated serum levels of IL-6, hs-CRP, and TNF-α compared to DWO. Importantly, these inflammatory markers showed a positive correlation with Wagner grading, indicating that systemic inflammation increases with the severity of foot ulceration. In patients with DFU in comparison with DWO, a higher plasma level of IL-6 could be linked to foot ulcer pathogenesis by micro-vascular and inflammatory mechanisms (16). Scheller et al (2021)', studied on the pro- and anti-inflammatory properties of the cytokine interleukin-6. It is a review article and concluded that IL-6 is involved not only in the activation of the immune system but also in regenerative processes as well as in the regulation of metabolism, in the maintenance of bone homeostasis, and in many neural functions (16).

C-reactive protein (CRP), a hepatic-originated plasma protein, is a key element of any inflammatory reaction. As a result of tissue damage or infection, the plasma levels of CRP may rapidly increase to more than 1000-folds above normal values, therefore it is widely used a monitor marker in the acute phase, responding to tissue damage, infection and inflammation in routine clinic. Increased hs-CRP levels, a general marker of systemic inflammation, further underscore the pro-inflammatory state in patients with advanced DFUs. We found that DFU had significantly elevated serum levels of hs-CRP compared to DWO. Studies have shown that elevated CRP levels are associated with diabetes .CRP, IL-1β, IL-6 and TNF-α level were higher in diabetic patient without foot lesion (PC) when Compared to Healthy Controls, and its level was higher in patient with Diabetic Foot Lesion when compared to PC(17). Elevated TNF-α and IL-6 levels are known to interfere with angiogenesis, collagen synthesis, and fibroblast activity, all of which are essential for proper wound repair. (18)

TNF-α may act as local intensification signals in pathological processes associated with chronic inflammation (19).A high dose of TNF α induces the increase of apoptosis, a mechanism of physiological cell death, in vitro. In this study, we found that DFU had significantly elevated serum levels of TNF-α compared to DWO. Previous studies have observed significant increased plasma levels of TNF α in DFU patient as compared with DWO, indicating immune inflammatory activation in such patients. (20)

Our findings are consistent with previous research highlighting the role of chronic inflammation in the pathogenesis of diabetic complications, particularly impaired wound healing. Our study not only confirms these associations but also demonstrates a graded increase of these markers across Wagner stages, adding strength to their potential use as clinical biomarkers. A study on ssystematic review and meta-analysis on the efficacy of inflammatory markers in diagnosing infected diabetic foot ulcers and diabetic foot osteomyelitis concluded that CRP is the ideal marker for diagnosing grade 2 DFU from non-infected DFU and CRP is the best markers for diagnosing grade 2 and grade 3 DFU(21).

In addition to inflammation, we observed that patients with DFUs had higher HbA1c levels, indicating poor glycaemic control. This finding is in line with the understanding that hyperglycaemia impairs immune function and delays wound healing, further contributing to ulcer severity. Lifestyle factors like smoking and alcohol use were also more prevalent in the DFU group, reinforcing the need for comprehensive patient education and lifestyle modification. All of these elements and molecular markers play an important role in extending the healing of diabetic ulcerated wounds and can be used as diagnostic tools by researchers to detect patients suffering from DFU .

CONCLUSION

This study underscores the systemic inflammation marked by elevated TNF-α,IL-6,and hs-CRP as a central mechanism driving the DFU onset progression. These markers not only correlate with ulcer severity but also offer promise for early detection, prognosis and diagnosis. Targeting the inflammatory pathway may enhance the therapeutic outcomes and reduce complications associated with DFU.

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REFERENCES

1. Zubair M, Malik A, Ahmad J. Plasma adiponectin, IL-6, hsCRP, and TNF-α levels in subject with diabetic foot and their correlation with clinical variables in a North Indian tertiary care hospital. Indian journal of endocrinology and metabolism. 2012 Sep 1;16(5):769-76.
2. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. Jama. 2005 Jan 12;293 (2):217-28.
3. Ahmada J, Zubairb M, Malikc A, Siddiquid MA, Wangnood SK. Cathepsin-D, Adiponectin, TNF-, IL-6 and hsCRP plasma levels in subjects with diabetic foot and possible correlation with clinical variables: A multicentric study. The Foot. 2012;22: 194-9.
4. Jeffcoate WJ, Game F, Cavanagh PR. The role of proinflammatory cytokines in the cause of neuropathic osteoarthropathy (acute Charcot foot) in diabetes. The Lancet. 2005 Dec 10;366 (9502):2058-61.

5. Bouhon AJ. The diabetic foot: from art to science. Diabetologia. 2004;47 (5):1343-53.
6. Roghmann MC, Siddiqui A, Plaisance K, Standiford H. MRSA colonization and the risk of MRSA bacteraemia in hospitalized patients with chronic ulcers. Journal of Hospital Infection. 2001 Feb 1;47(2):98-103.
7. Armstrong DG, Liswood PJ, Todd WF. Prevalence of mixed infections in the diabetic pedal wound a retrospective review of 112 infections. JOURNAL-AMERICAN PODIATRIC MEDICAL ASSOCIATION. 1995;85:533-538
8. Gadepalli R, Dhawan B, Sreenivas V, Kapil A, Ammini AC, Chaudhry R. A clinico-microbiological study of diabetic foot ulcers in an Indian tertiary care hospital. Diabetes care. 2006 Aug 1; 29 (8):1727-32.
9. Murray HJ, Young MJ, Boulton AJM. The relationship between callus formation, high pressures and neuropathy in diabetic foot ulceration. Diab Med 1996 Nov; 13(11):979-982.
10. Boulton AJ. The diabetic foot: from art to science. The 18th Camillo Golgi lecture. Diabetologia. 2004 Aug; 47(8):1343-53.
11. Ye D, Zhu J, Su S, Yu Y, Zhang J, Yin Y, Lin C, Xie X, Xiang Q, Yu R. Natural small molecules regulating the mitophagy pathway counteract the pathogenesis of diabetes and chronic complications. Frontiers in Pharmacology. 2025 Apr 16;16: 1571767.
12. Taher MT, Moradi S, Azizi MR, Shekarabi M, Barati M. Procalcitonin in diagnosing the diabetic foot infection. Archives of Clinical Infectious Diseases. 2011 Apr 30;6(2)
13. Nicholson SE, Metcalf D, Sprigg NS, Columbus R, Walker F, Silva A et al. Suppressor of cytokine signaling (SOCS)-5 is a potential negative regulator of epidermal growth factor signaling. Proceedings of the National Academy of Sciences. 2005 Feb 15;102(7):2328-33.
14. Kojima S, Yamada T, Tamai M. Quantitative analysis of interleukin-6 in vitreous from patients with proliferative vitreoretinal diseases. Japanese journal of ophthalmology. 2001 Jan 1;45(1):40-5
15. Wang Y, Liu Y, Zhang L, Zhang Y, Li Y, Liu G. The association between IGF-1 and diabetic foot ulcer: a systematic review and meta-analysis. Int J Endocrinol ;2020: 9659730.
16. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro-and anti-inflammatory properties of the cytokine interleukin-6. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2011 May 1;1813(5):878-88.
17. McFadyen JD, Kiefer J, Braig D, Loseff-Silver J, Potempa LA, Eisenhardt SU et al. Dissociation of C-reactive protein localizes and amplifies inflammation: evidence for a direct biological role of C-reactive protein and its conformational changes. Frontiers in immunology. 2018 Jun 12; 9: 1351.
18. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. Wound repair and regeneration. 2008 Sep;16(5):585-601.
19. Santana RB, Xu L, Chase HB, Amar S, Graves DT, Trackman PC. A role for advanced glycation end products in diminished bone healing in type 1 diabetes. Diabetes. 2003 Jun 1;52 (6):1502-10.
20. Balasubramanyam M, Rema M, Premanand C. Biochemical and molecular mechanisms of diabetic retinopathy. Current Science. 2002 Dec 25:1506-14.
21. Sharma H, Sharma S, Krishnan A, Yuan D, Vangaveti VN, Malabu UH et al,. The efficacy of inflammatory markers in diagnosing infected diabetic foot ulcers and diabetic foot osteomyelitis: Systematic review and meta-analysis. PloS one. 2022 Apr 27;17(4):e0267412.