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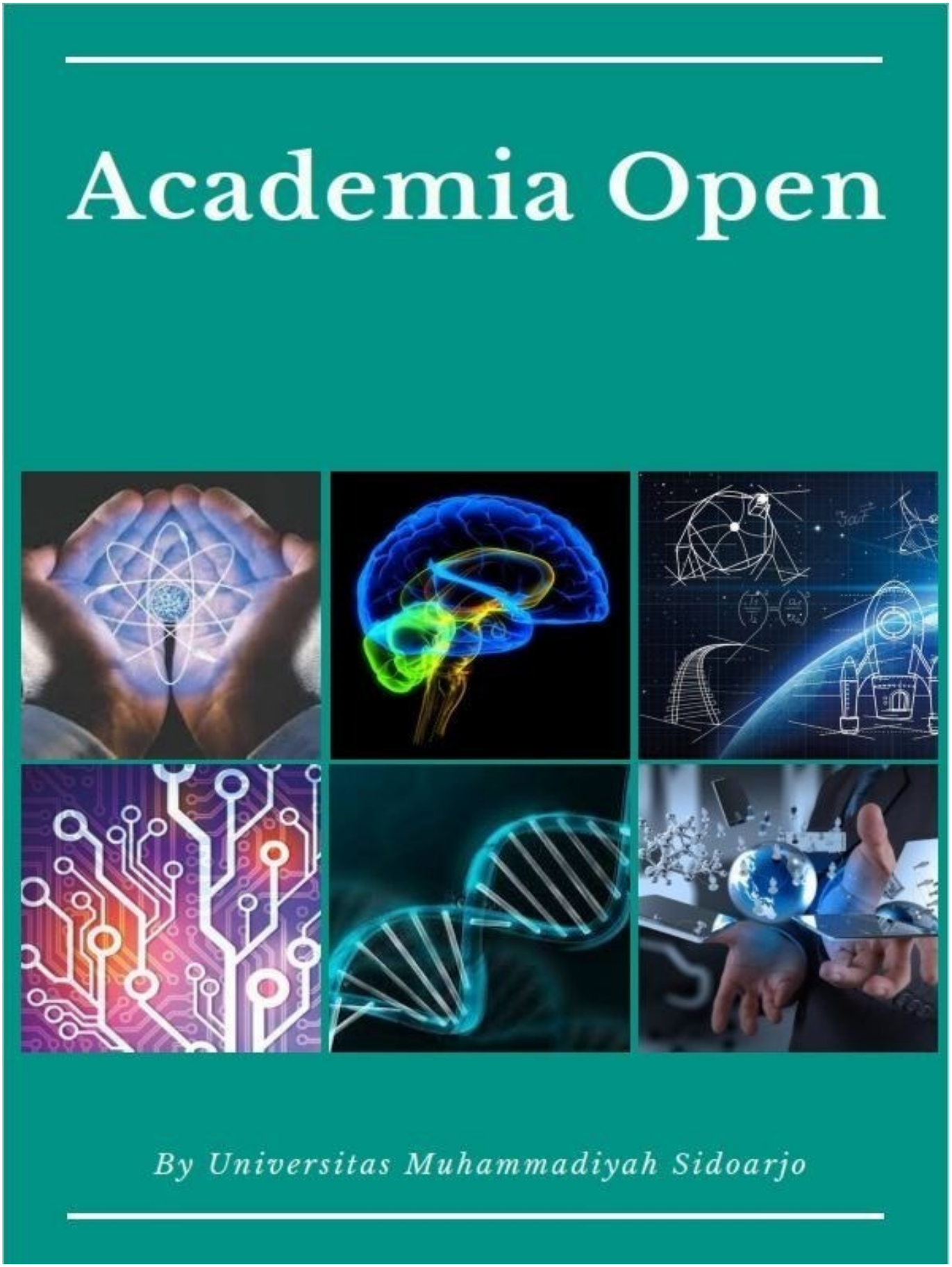

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Monitoring of IL-1β and MCP-1 Levels in Diabetic Patients with Foot Ulcer Infections

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Abstract

General Background: Diabetic foot ulcers (DFUs) are among the most severe complications of diabetes mellitus, often complicated by persistent infections that delay healing and increase morbidity. Specific Background: Chronic DFUs are associated with exaggerated inflammatory responses, where cytokines such as interleukin-1β (IL-1β) and monocyte chemoattractant protein-1 (MCP-1) play pivotal roles in tissue damage and impaired recovery. Knowledge Gap: Despite evidence linking cytokines to inflammation, their diagnostic and prognostic utility in monitoring infection severity and bacterial involvement in DFUs remains insufficiently explored. Aims: This study evaluated serum IL-1β and MCP-1 levels in diabetic patients with infected foot ulcers, examining associations with ulcer severity, gender, and microbial isolates. Results: Compared with healthy controls, diabetic patients exhibited significantly elevated IL-1β and MCP-1 levels, which strongly correlated with each other and increased with Wagner ulcer stage. Staphylococcus aureus was the predominant bacterial isolate, followed by E. coli and P. aeruginosa. Gender-specific differences were observed, with males showing higher cytokine concentrations, while correlations were stronger among females. Novelty: The study demonstrates a clear link between pro-inflammatory cytokines and ulcer severity, highlighting their potential as biomarkers for disease monitoring. Implications: Incorporating IL-1β and MCP-1 assessments into clinical practice may improve early diagnosis, guide therapeutic strategies, and support personalized management of diabetic foot infections.

Highlight :

- IL-1β and MCP-1 increase with ulcer severity as reliable biomarkers.
- Staphylococcus aureus dominates bacterial isolates in diabetic foot ulcers.
- Persistent inflammation delays proper wound healing.

Keywords : Diabetic Foot Ulcer, IL-1β, MCP-1, Inflammatory Cytokines, Wound Healing

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Introduction

Diabetes mellitus (DM) is an acknowledged worldwide distributed chronic metabolic disorder having elevated glucose levels in the blood in the long run stemming either from deficiency in insulin secretion, insulin action or both [1][2]. Of the many complications, diabetic foot ulcer (DFU) infections are among the most devastating and expensive to treat, typically resulting in extended hospitalization, lower-extremity amputation, and substantial deterioration of quality of life. The World Health Organization (WHO) projected that 15% of people with diabetes will have a diabetic foot ulcer during the course of their lifetime, and infection is a complication that is frequent and has a significant impact [3].

The pathophysiology of DFU is multifactorial and includes neuropathy, peripheral arterial disease (PAD), immunosuppression, and delay in wound healing [4]. An exaggerated and dysregulated inflammatory response is one of the most important factors contributing to the chronicity and severity of DFUs. In this respect, pro-inflammatory cytokines and chemoattractants have a central function in the development of tissue destruction, infection with microbes and delayed wound repair. Two important mediators in the inflammatory cascade of diabetic wounds are IL-1β and MCP-1 [5][6].

IL-1β is a strong pro-inflammatory cytokine that is mainly synthesized by activated macrophages in response to microbial components as well as cellular damage. It is important in triggering and amplifying inflammation by stimulating the expression of adhesion molecules, chemokines, and other cytokines. High levels of IL-1β have also been observed during different chronic inflammatory diseases, such as complications from diabetes (nephropathy, retinopathy, and foot ulcers). Elevated IL-1β levels were reported in DFUs and linked to poor healing and worse clinical prognosis, presumably because of its involvement in sustained inflammation and tissue damage [7][8].

MCP-1, or CCL2, is a chemokine that recruits monocytes, memory T cells, and dendritic cells to the sites of infection or tissue injury. It is synthesized by many cell types, such as endothelial cells, fibroblasts and macrophages, after inflammatory stimuli [9]. MCP-1 is elevated in patients with diabetes and has been involved in the development of diabetes complications by enhancing leukocyte recruitment and maintained inflammatory responses. It have been reported that elevated-levels of MCP-1 can intensify local inflammation at chronic wounds area, which in turn delays their wound recovery [10].

The dynamic monitoring of IL-1β and MCP-1 in DFU infection patients may have a significantly important diagnostic and prognostic role in wound swelling, progression, and therapeutic strategy. Though clinical assessment is often based on visual inspection, microbiological culture and clinical scores, they tend to be limited in terms of information provided on ulcer inflammation [11]. Consequently, the addition of molecular biomarkers (e.g., IL-1β and MCP-1) may improve diagnostic accuracy, therefore, facilitate more appropriate decisions for intervention and potentially the prediction of wound healing [12].

We now investigated the serum values of IL-1β and MCP-1 in diabetic patients suffering from infected foot ulcers in order to assess its relationship with ulcer severity and microbial profile. This study attempts to provide potential biomarkers for the monitoring of pathologic progression, for a more efficient clinical management strategy in diabetic wound care, by unveiling the inflammatory mechanism of DFUs.

Methodology

A cross-sectional observational study that took place at the Nasiryah General Hospital, from January to June 2024 in conjunction with the Diabetic Foot Unit of Nasiryah General Hospital, Iraq. One hundred diabetic patients with clinically diagnosed foot ulcer infection and 50 healthy subjects without diabetes or any active infection were recruited. For diabetic patients, the inclusion criteria consisted of a verified type 2 diabetes mellitus, a history of foot ulcers classified according to the Wagner classification (Stage 1-3 stages), and no other chronic inflammatory or autoimmune diseases. Excluded were: antibiotic therapy over the previous two weeks, absence of consent, active malignancy, stage V renal failure. Informed consent was obtained from all the subjects before collection of the samples. Venous blood (5 mL) was collected aseptically from each subject. The obtained blood was centrifuged at 3000 rpm for 10 min for separation of serum, and was stored at −20°C until the analysis. Serum IL-1β and MCP-1 were detected by ELISA with commercially available kits according to the manufacturer's instructions. Bacterial isolates from foot ulcer swab items were inoculated using a sterile cotton swab to the freshly prepared blood agar, MacConkey agar, and nutrient agar plates and incubated aerobically at 37°C for 24–48 hours. All bacterium isolates were confirmed through routine biochemistry tests. The data were analysed to compare cytokine levels in groups, to find correlations between IL-1β and MCP-1 and to investigate the relationship between these and ulcer severity and microbial isolates.

Statistical analysis

Statistical analysis of the quantitative data was performed using SPSS software version 26. Descriptive results were expressed as frequencies and percentages. For variables with a normal distribution, independent and paired t-tests (two-tailed) were utilized. In cases where the data were not normally distributed, non-parametric tests such as the Mann-Whitney U test, Wilcoxon signed-rank test, and Chi-square test were applied as appropriate. A p-value of less than 0.05 was considered indicative of statistical significance.

Ethical approval

The study was approved by the Human Ethics Committee of Nasiriyah General Hospital. All participants were informed about the study and gave written informed consent before enrollment. Confidentiality of patient information was strictly ensured throughout the research.

Results

Comparison of Sociodemographic and Clinical Characteristics Between Diabetic Patients and Healthy Controls

The study results showed that the mean age of diabetic patients was 33.8 ± 4.5 years compared to 32.9 ± 4.2 years in healthy individuals, with no statistically significant differences ($p = 0.28$). No significant differences were recorded between the two groups in terms of the distribution of males and females, as the percentage in the diabetic group was 60% males and 40% females, compared to 60% males and 40% females in the control group ($p = 0.94$). In contrast, a significant difference was observed in the body mass index (BMI), as it was significantly higher in diabetic patients (29.7 ± 3.6 kg/m²) compared to healthy controls (24.2 ± 2.8 kg/m²) ($p < 0.001$). The results also showed that the percentage of smokers was higher in the diabetic group (32%) compared to healthy controls (18%), and this difference was statistically significant ($p = 0.03$). Regarding the duration of diabetes, the average was 9.2 ± 2.7 years, while this variable was not measured in the control group (Table 1).

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Table 1: Assessment of Age, Gender, BMI, Smoking Status, and Duration of Diabetes

Characteristic	Diabetic Patients (n = 100)	Healthy Controls (n = 50)	p-value
Age (years)	33.8 ± 4.5	32.9 ± 4.2	0.28
Gender (Male/Female)	60 / 40	30 / 20	0.94
BMI (kg/m²)	29.7 ± 3.6	24.2 ± 2.8	<0.001
Smoking Status (%)	32%	18%	0.03
Duration of Diabetes (years)	9.2 ± 2.7	–	–

Comparison of Interleukin-1β (IL-1β) Levels Among Diabetic Patients and Healthy Controls

The study results showed a significant increase in the mean concentration of interleukin-1β (IL-1β) in diabetic patients compared to healthy individuals. The mean concentration in all diabetic patients was 41.2 ± 10.3 pg/ml, compared to 19.6 ± 6.7 pg/ml in the control group. This difference was highly statistically significant ($p < 0.001$). The mean concentration of IL-1β was also higher in diabetic males (42.7 ± 10.5 pg/ml) compared to diabetic females (39.1 ± 9.8 pg/ml), suggesting gender differences in the inflammatory response within the diabetic group, although the p-value between males and females was not indicated. These findings reflect the potential role of IL-1β as an inflammatory marker associated with diabetes and may contribute to understanding gender differences in this context (Table 2).

Table 2: Serum IL-1β Concentrations in Diabetic Males, Females, and Healthy Individuals

Group	Mean IL-1β (pg/mL) ± SD	p-value
Diabetic Males (n=60)	42.7 ± 10.5	<0.001
Diabetic Females (n=40)	39.1 ± 9.8	
All Diabetic Patients	41.2 ± 10.3	
Healthy Controls (n=50)	19.6 ± 6.7	

Comparison of Monocyte Chemoattractant Protein-1 (MCP-1) Levels Among Diabetic Patients and Healthy Controls

The study results showed a significant increase in the mean concentration of monocyte chemoattractant protein-1 (MCP-1) in diabetic patients compared to healthy individuals. The mean concentration in all diabetic patients was 498.6 ± 88.4 pg/ml, compared to 263.5 ± 75.1 pg/ml in the control group. The difference was highly statistically significant ($p < 0.001$). Regarding gender distribution, the mean MCP-1 concentration was higher in diabetic males (511.4 ± 90.2 pg/ml) compared to diabetic females (478.3 ± 84.7 pg/ml), suggesting gender differences in MCP-1 levels within the diabetic group, although a p-value for comparing males and females was not available. These data reflect the important role of MCP-1 in the inflammatory response associated with diabetes and may contribute to explaining biological differences between the sexes (Table 3).

Table 3: Serum MCP-1 Concentrations in Diabetic Males, Females, and Non-Diabetic Individuals

Group	Mean MCP-1 (pg/mL) ± SD	p-value
Diabetic Males (n=60)	511.4 ± 90.2	<0.001
Diabetic Females (n=40)	478.3 ± 84.7	
All Diabetic Patients	498.6 ± 88.4	
Healthy Controls (n=50)	263.5 ± 75.1	

Correlation Between IL-1β and MCP-1 Levels Among Diabetic Patients

Pearson correlation analysis results showed a highly significant positive correlation between IL-1β and MCP-1 levels in diabetic patients. The correlation coefficient for all patients was ($r = 0.63$, $p < 0.001$), indicating that an increase in one marker is associated with an increase in the other. When the relationship was analyzed by gender, a moderate correlation was observed in affected males ($r = 0.59$, $p < 0.001$), while it was stronger in affected females ($r = 0.67$, $p < 0.001$), reflecting a gender-specific variation in the intensity of the relationship between the two inflammatory markers. These results suggest a close interaction between IL-1β and MCP-1 in the inflammatory context associated with diabetes, and this interaction may play a role in the development of disease complications (Table 4).

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Table 4: Pearson Correlation Analysis in All Patients and by Gender Subgroups

Variable Pair	Pearson Correlation (r)	p-value
IL-1β vs. MCP-1 (All patients)	0.63	<0.001
IL-1β vs. MCP-1 (Males only)	0.59	<0.001
IL-1β vs. MCP-1 (Females only)	0.67	<0.001

Association of Inflammatory Markers with Diabetic Foot Ulcer Severity (Wagner Classification)

The study results revealed a direct relationship between the severity of diabetic foot ulcers (according to the Wagner classification) and the levels of the inflammatory markers IL-1β and MCP-1. The mean IL-1β concentration gradually increased with increasing ulcer severity, reaching 36.8 ± 7.9 pg/ml in patients with grade 1, 42.5 ± 9.2 pg/ml in grade 2, and 47.6 ± 8.5 pg/ml in grade 3, with a statistically significant difference ($p < 0.001$). Similarly, MCP-1 levels increased from 455.2 ± 70.1 pg/ml in grade 1 to 498.4 ± 88.3 pg/ml in grade 2, and 552.3 ± 95.2 pg/ml in grade 3, and this increase was also statistically significant ($p < 0.001$). These findings reflect a strong relationship between ulcer severity and the level of inflammation, supporting the role of IL-1β and MCP-1 as potential biomarkers for monitoring the progression of diabetic foot ulcers (Table 5).

Table 5: Serum IL-1β and MCP-1 Levels Across Wagner Grades 1 to 3

Severity Group (Wagner Grade)	IL-1β (pg/mL) ± SD	MCP-1 (pg/mL) ± SD	p-value (IL-1β)	p-value (MCP-1)
Grade 1 (n=35)	36.8 ± 7.9	455.2 ± 70.1		
Grade 2 (n=40)	42.5 ± 9.2	498.4 ± 88.3		
Grade 3 (n=25)	47.6 ± 8.5	552.3 ± 95.2	<0.001	<0.001

Distribution of Bacterial Isolates from Diabetic Foot Infections

Bacterial isolation results from diabetic foot ulcers showed a diversity of pathogenic species. The most common species was Staphylococcus aureus, accounting for 28% (28 isolates), followed by Escherichia coli, accounting for 20% (20 isolates), and Pseudomonas aeruginosa, accounting for 15% (15 isolates). Klebsiella pneumoniae was also isolated, accounting for 12% and Proteus mirabilis for 10%. Enterococcus faecalis was also isolated, accounting for 8% and Streptococcus pyogenes for 5%. Acinetobacter baumannii was the least prevalent, accounting for only 2%. These results reflect the dominance of Gram-positive bacteria, particularly S. aureus, along with the presence of resistant Gram-negative bacteria such as P. aeruginosa and K. pneumoniae, highlighting the importance of accurate diagnosis and appropriate antibiotic selection in treating such cases (Table 6).

Table 6: Frequency and Percentage of Isolated Pathogens Among 100 Samples

Bacterial Species	No. of Isolates (n=100)	Percentage (%)
Staphylococcus aureus	28	28%
Escherichia coli	20	20%
Pseudomonas aeruginosa	15	15%
Klebsiella pneumoniae	12	12%
Proteus mirabilis	10	10%
Enterococcus faecalis	8	8%
Streptococcus pyogenes	5	5%
Acinetobacter baumannii	2	2%

Discussion

In the present study, of 100 diabetic foot infection (DFI) specimens C&S culture revealed; Staphylococcus aureus was the most commonly isolated infecting organism (28%), followed by E. coli (20%), P. aeruginosa (15%), K. pneumoniae (12%), P. mirabilis (10%), E. faecalis (8%), S. pyogenes (5%), and A. baumannii (2%). The polymicrobial nature of DFIs is evident from these results thereby indicating the predominance of both Gram-positive and Gram-negative bacteria [13].

Our findings are consistent with findings by Lipsky and co-workers, which reported S. aureus to be the most common organism responsible for causing DFIs, including methicillin-resistant S. aureus (MRSA), attributed to S. aureus's ability to colonize the skin as well as promote tissue invasion in immune-compromised individuals [14]. Similarly, the investigation by also found S. aureus and E. coli as the most common organism.

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These similar features may be underlined by the shared pathophysiology found in DFIs among populations, including neuropathy, poor glycemia and vascular deficit and which encourage colonization by these etiology germ [15].

By contrast, other studies have found other predominant organisms. For instance, in a study conducted by reported P. aeruginosa as the most common organism in DFIs, even more than S. aureus [16]. Similarly, a Nigerian research conducted by Onile and others revealed higher occurrence of K. pneumoniae and Proteus [17][18]. Such variation may be due to differences in local microbial ecology, practices of antibiotic use, hospital hygiene and environmental factors like those influenced by climatic factors that influence the survival and transmission of bacteria [19].

One possible reason of the high frequency of S. aureus in our series could be due to its body carriage as a normal skin flora, thus it is a common colonizer of open wounds, in particularly patients with impaired immune responses such as diabetics [20][21]. Patients with diabetes are also frequently hospitalized or attend health care facilities, in which colonization with resistant strains such as MRSA is endemic [22]. The preponderance of E. coli and K. pneumoniae, two enteric bacterial type, might indicate besides fecal contamination from the GI tract; assuming that in some cases suspected-patients might have poor hygiene or urinary or fecal incontinence [23].

The presence of P. aeruginosa and Acinetobacter baumannii, which are opportunistic, multidrug-resistant pathogens frequently involved in nosocomial infections, indicates the possibility of hospital-acquired infection (HAI) or long-term colonization of the wound. P. aeruginosa is resident of damp situations and is notorious for being resistant to several antibiotics, resulting in a complex treatment [24]. The low rate of A. baumannii (2%) might be indicative for the low-endemic status of A. baumannii in our setting, but with a high affected clinical impact in view of resistance.

Variation in bacterial isolates seen in our study re-emphasizes the polymicrobial character of DFIs as reported previously [25]. Clinicians must therefore depend upon reliable microbiological diagnosis and sensitivity testing to direct antimicrobial therapy in this polymicrobial setting. Empirical therapy in the absence of culture results may result in treatment failure, enhanced resistance, and suboptimal response [26].

Heterogeneity in bacterial yield between studies may be due to differences in methodological construct. For example, studies relying only on swab cultures may overlook deeper organisms, when contrasted with those using tissue biopsies [27]. Furthermore, ulcer characteristics for example, severity of the ulcer, prior antibiotic treatment and history of hospitalization have an impact on culture outcome. Although practical, our use of swab sampling may have led to reduced detection of anaerobic organisms and further pathogens [28].

In addition, E. faecalis and S, pyogenes were also observed, albeit at lower prevalence, which matches with the fact that they are identified as secondary invaders and as part of mixed infections in chronic wounds [29]. Their presence supports the need for broad-spectrum coverage, particularly in severe and non-healing ulcers, until culture-based treatment is achieved [30].

Conclusion

Results of the present study demonstrate the importance of IL-1β and MCP-1as predictive biomarkers in monitoring diabetic foot ulcer (DFU) infections. All diabetic patients had increased levels of both cytokines, and there was a significant correlation between the severity of the ulcer stage and the amount of cytokine present, indicating an obvious relationship between inflammation and the clinical severity of the wound. All of which supports the idea that these inflammatory markers should be considered as valuable predictors of the disease progression which can be used in the clinical setting to predict potential complications and possibly even improve clinical management. Specific bacterial pathogens, such as Staphylococcus aureus, were more prevalent in these infections, emphasizing the importance of localized knowledge of microbial profiles to drive targeted antimicrobial therapy. Therefore, further studies are needed to broaden the application of molecular tools, such as anaerobic cultures and more extensive identification of pathogens to study the polymicrobial aspects of DFUs. Moreover, studying the response at sex level and the interplay of inflammation and bacterial composition and diversity may elucidate more tailored diagnosis and treatment of diabetic foot infection.

References

1. D. Lateef, N. Nasser, and O. Mohsein, "The Relationships Between Aplein, Vaspin and Thyroid Hormone Levels in Obese Diabetic and Non-Diabetic Women," J. Exp. Clin. Med., vol. 41, no. 2, pp. 239-245, 2024, doi: 10.1016/j.jecm.2024.02.010.
2. N. A. Abdulmuttaleb, M. Q. Mohammed, and O. A. Mohsein, "The Impact of Adipocytokines on Thyroid Function and Obesity: A Narrative Review," Development, vol. 8, p. 9, 2024.
3. E. W. Gregg et al., "Improving Health Outcomes of People With Diabetes: Target Setting for the WHO Global Diabetes Compact," Lancet, vol. 401, no. 10384, pp. 1302-1312, 2023, doi: 10.1016/S0140-6736(23)00516-8.
4. J. Kim, "The Pathophysiology of Diabetic Foot: A Narrative Review," J. Yeungnam Med. Sci., vol. 40, no. 4, pp. 328-334, 2023, doi: 10.12701/jyms.2023.00948.
5. J. M. Raja et al., "Diabetic Foot Ulcer: A Comprehensive Review of Pathophysiology and Management Modalities," World J. Clin. Cases, vol. 11, no. 8, pp. 1684-1698, 2023, doi: 10.12998/wjcc.v11.i8.1684.
6. V. Ramachandran et al., "Physiological and Pathophysiological Aspects of Diabetic Foot Ulcer and Its Treatment Strategies," Curr. Diabetes Rev., vol. 19, no. 8, pp. 127-139, 2023, doi: 10.2174/1573399819666220809114635.
7. A. Marrocco and L. A. Ortiz, "Role of Metabolic Reprogramming in Pro-Inflammatory Cytokine Secretion From LPS or Silica-Activated Macrophages," Front. Immunol., vol. 13, p. 936167, 2022, doi: 10.3389/fimmu.2022.936167.

8. Q. Mo et al., "Regulation of Osteogenic Differentiation by the Pro-Inflammatory Cytokines IL-1β and TNF-α: Current Conclusions and Controversies," Hum. Cell, vol. 35, no. 4, pp. 957-971, 2022, doi: 10.1007/s13577-022-00789-1.
9. K. Kim et al., "Materials and Cytokines in the Healing of Diabetic Foot Ulcers," Adv. Ther., vol. 4, no. 9, p. 2100075, 2021, doi: 10.1002/adtp.202100075.
10. A. H. Hamad, H. M. Mustafa, and O. A. Mohsein, "Detection of the Levels of Immune Cytokines (IL4, IL5, TNF-α) in School-Age and Preschoolers With an Ascaris Lumbricoides Infection," J. Parasitic Dis., vol. 48, no. 4, pp. 782-787, 2024, doi: 10.1007/s12639-023-01629-0.
11. M. Ejiugwo et al., "The Development of a Direct Co-Culture-Based Model for Diabetic Foot Ulcer Mimicking Inflammation and Impaired Phagocytosis," In Vitro Models, pp. 1-19, 2025, doi: 10.1007/s44164-025-00028-6.
12. M. R. Sai Samanvitha et al., "Progressive Hydrogel Applications in Diabetic Foot Ulcer Management: Phase-Dependent Healing Strategies," J. Drug Deliv. Sci. Technol., vol. 80, p. 105118, 2025, doi: 10.1016/j.jddst.2025.105118.
13. C. R. Chaves et al., "Multidrug-Resistant Staphylococcus Aureus in Diabetic Foot Infections (DFI) From Beira, Mozambique: Prevalence and Virulence Profile," Infect. Drug Resist., vol. 31, pp. 2779-2796, 2025, doi: 10.2147/IDR.S453216.
14. Z. Khamis Abbas et al., "Immunological Biomarkers and Their Role in the Diagnosis and Prognosis of Leishmaniasis: A Case–Control Study," Trop. Parasitol., vol. 15, no. 1, pp. 33-41, 2025, doi: 10.4103/tp.tp_68_23.
15. J. Lee et al., "The Bacteriology of Diabetic Foot Ulcers and Infections and Incidence of Staphylococcus Aureus Small Colony Variants," J. Med. Microbiol., vol. 72, no. 6, article 001716, Jun. 2023, doi: 10.1099/jmm.0.001716.
16. N. A. Abdulmuttaleb, M. Q. Mohammed, and O. A. Mohsein, "Exploring the Connection Between Inflammatory Cytokines, Hypertension, and Diabetes in Angina Patients," Cytokines, vol. 14, no. 15, p. 16, 2024.
17. O. Bajt, "From Plastics to Microplastics and Organisms," FEBS Open Bio, vol. 11, no. 4, pp. 1190-1205, 2021, doi: 10.1002/2211-5463.13116.
18. J. Kaushal, M. Khatri, and S. K. Arya, "Recent Insight Into Enzymatic Degradation of Plastics Prevalent in the Environment: A Mini-Review," Cleaner Eng. Technol., vol. 4, p. 100187, 2021, doi: 10.1016/j.clet.2021.100187.
19. R. Q. Taha et al., "Bacterial Aetiologies of Otitis Media and Their Antimicrobial Susceptibility in Ear Swab Culture," Int. J. Biol. Sci., vol. 6, no. 1, pp. 94-99, 2024.
20. L. N. McEwen and W. H. Herman, "Health Care Utilization and Costs of Diabetes," Diabetologia, vol. 64, no. 12, pp. 2749-2757, 2021, doi: 10.1007/s00125-021-05554-3.
21. D. Barsasella et al., "Predicting Length of Stay and Mortality Among Hospitalized Patients With Type 2 Diabetes Mellitus and Hypertension," Int. J. Med. Inform., vol. 154, article 104569, Oct. 2021, doi: 10.1016/j.ijmedinf.2021.104569.
22. H. Jalilian et al., "Forgone Care in Patients With Type 2 Diabetes: A Cross-Sectional Study," BMC Public Health, vol. 21, no. 1, article 1588, Aug. 2021, doi: 10.1186/s12889-021-11602-6.
23. M. G. Nanna et al., "Use of Sodium-Glucose Cotransporter 2 Inhibitors and Glucagonlike Peptide-1 Receptor Agonists in Patients With Diabetes and Cardiovascular Disease in Community Practice," JAMA Cardiol., vol. 8, no. 1, pp. 89-95, Jan. 2023, doi: 10.1001/jamacardio.2022.4390.
24. W. Y. Agyeman et al., "A Systematic Review of Antibiotic Resistance Trends and Treatment Options for Hospital-Acquired Multidrug-Resistant Infections," Cureus, vol. 14, no. 10, Oct. 2022, doi: 10.7759/cureus.29920.
25. E. Odoyo et al., "Environmental Contamination Across Multiple Hospital Departments With Multidrug-Resistant Bacteria Pose an Elevated Risk of Healthcare-Associated Infections in Kenyan Hospitals," Antimicrob. Resist. Infect. Control, vol. 12, no. 1, article 22, Mar. 2023, doi: 10.1186/s13756-023-01274-7.
26. N. H. Naif et al., "The Impact of Inflammatory and Adipokine Biomarkers on Breast Cancer Progression and Patient Outcomes," Bull. Pharm. Sci. Assiut Univ., vol. 48, no. 1, pp. 511-522, 2025.
27. H. Sun et al., "Microbiological Distribution, Antimicrobial Susceptibility and Risk Factors of Polymicrobial Infections in Diabetic Foot," Clin. Lab., vol. 70, no. 4, Apr. 2024, doi: 10.7754/Clin.Lab.2023.230829.

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12708

28. A. Garre et al., "Critical Comparison of Statistical Methods for Quantifying Variability and Uncertainty of Microbial Responses From Experimental Data," Int. J. Food Microbiol., vol. 383, article 109935, Dec. 2022, doi: 10.1016/j.ijfoodmicro.2022.109935.
29. A. A. Abdulhussien et al., "The Impact of Aspergillus Fumigatus on Cytokine Production and Biomarker Expression in Pulmonary Infections," Egypt. J. Med. Microbiol., vol. 35, no. 1, 2026.
30. M. Rohde and P. P. Cleary, "Adhesion and Invasion of Streptococcus Pyogenes Into Host Cells and Clinical Relevance of Intracellular Streptococci," in Streptococcus Pyogenes: Basic Biology to Clinical Manifestations, 2nd ed., Oklahoma City, OK, USA: University of Oklahoma Health Sciences Center, 2022.

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