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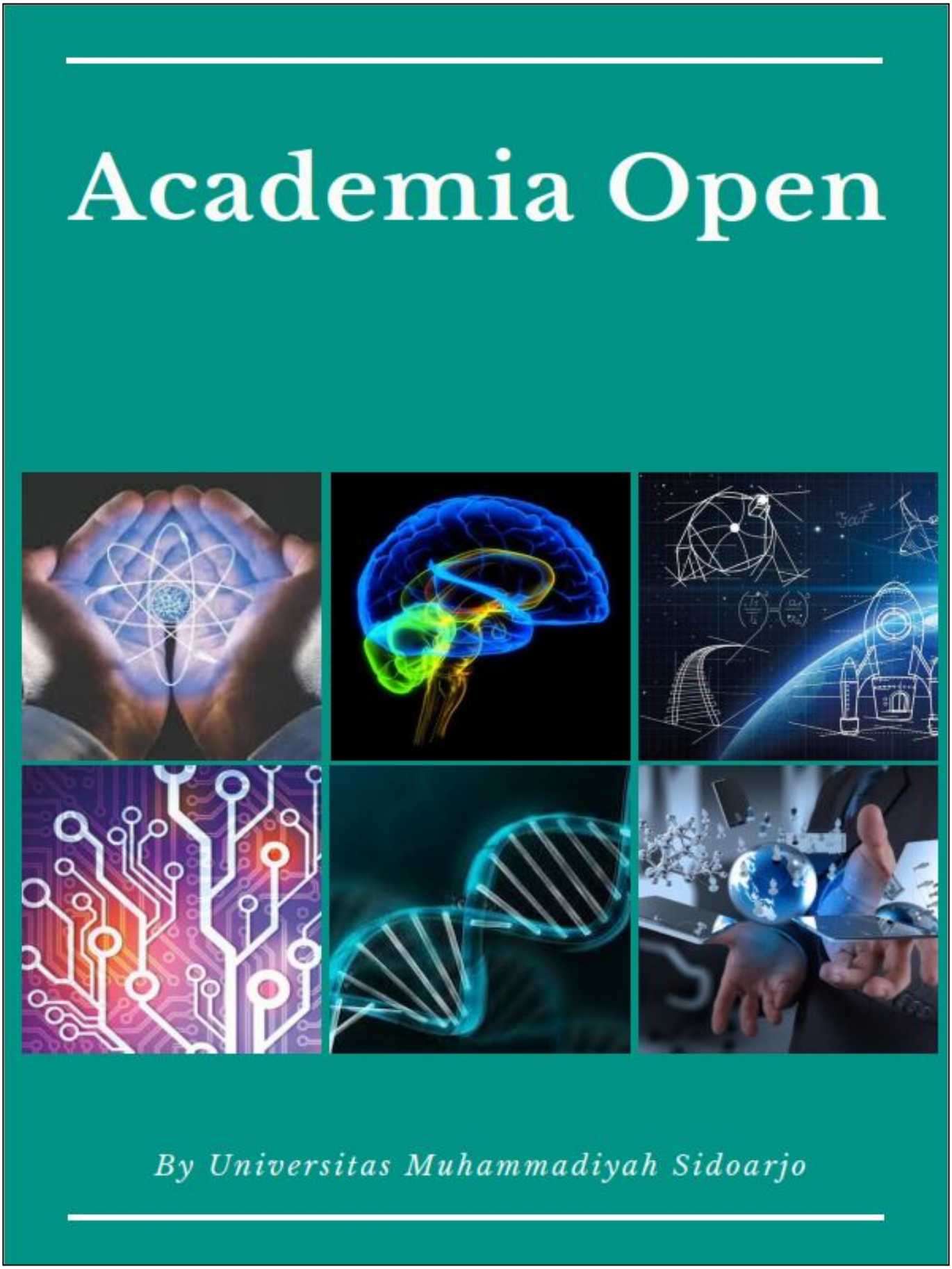

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Table Of Contents

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Monitoring of IL-1? and MCP-1 Levels in Diabetic Patients with Foot Ulcer Infections: Pemantauan Kadar IL-1? dan MCP-1 pada Pasien Diabetes dengan Infeksi Luka Kaki

Pemantauan Kadar IL-1? dan MCP-1 pada Pasien Diabetes dengan Infeksi Luka Kaki

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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

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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).

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	–	–

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

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).

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	

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

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).

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	

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

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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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

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

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).

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		

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