

How to Cite:

Katya, W. E., Salman, A. N., & Mohammed, A. G. (2022). Role of interleukin-6 in diabetic foot ulcers patients in Thi-Qar Province. *International Journal of Health Sciences*, 6(S9), 1499–1505.
<https://doi.org/10.53730/ijhs.v6nS9.12594>

Role of interleukin-6 in diabetic foot ulcers patients in Thi-Qar Province

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Abstract---The aim of this study is to evaluate the level of Interleukin-6 in patient with diabetic foot ulcers. The present study was carried out in the Diabetes and Endocrinology Center of the Health Directorate at Thi-Qar Province, at the period between January to July (2022). The immune status investigates for patients with diabetic foot ulcers by measuring the levels of Interleukin-6 (IL-6) in serum using a technique enzyme-linked immune Sorbent adsorptive (ELISA). The study included 100 subjects, (50) patients with diabetic foot and (50) were healthy control. The statistical analysis showed that a high significant increase ($P \leq 0.01$) in serum the rate of concentration of (IL-6) in patients (6.16 ± 5.24) pg/ml compared to the healthy control group (5.42 ± 7.74) pg/ml with significant difference (0.01). These results revealed that the excessive presence of (IL-6) might play a role in Thi-Qar Province population.

Keywords: Diabetes mellitus (DM), Diabetic Foot Ulcers (DFU), Interleukin-6 (IL-6).

1. Introduction

Diabetic Foot Ulcers (DFUs) is one of the most serious complications of diabetes mellitus and a main risk factor for plantar ulceration [1]. (DFUs) is an injury to all layers of skin that usually occur on the soles of the feet which including ulcerations, infections and gangrene, as a result of peripheral neuropathy or

peripheral arterial disease, poor glycemic control, foot deformity in diabetes mellitus (DM) patients [2]. Hyperglycemia causes tissue injury leading to vascular damage through generation of free radicals and their effect on endothelium in diabetics [3]. The consequence of DFUs is amputation. An estimated 52% to 68% of diabetic patients with amputation experienced stable frailty, loss of movement, and significant reduction in the lifespan. Inferior extremity amputations are greater in DM patients than in non-DM patients. A study by Ignatyeva et al showed the higher cost of medical care for DM patients with DFUs than those with no DFUs [4].

Diabetic foot wounds are marked by a persistent and dysregulated inflammatory phase, an enhanced production and release of pro-inflammatory cytokines such as (IL-1 β , IL-6 and TNF- α) causes disturbance the balance between pro-inflammatory and anti-inflammatory macrophages [5]. A chronic state of low-level inflammation is related with the pathogenesis of T2DM. This low-level inflammation represents itself, among other things, by elevated circulating levels of inflammatory cytokines such as interleukin 6 (IL-6). T-cells and macrophages secrete IL-6 which is a multifunctional cytokine in case of infection and inflammation to stimulate immune reaction. Indeed, this cytokine is involved in the inflammatory response associated with insulin-resistant state [6].

Interleukin-6 (IL-6) is one of the pro-inflammatory cytokines that can be detected in serum in the early stages of infection [7]. The highest levels of acute-phase markers and IL-6 were found in those patients with most features of the insulin resistance syndrome. Multifunction cytokine with 183 amino acids [3,6]. Through the review, this study was aimed to evaluate the level of Interleukin-6 in patient with diabetic foot ulcers.

2. Materials and Methods

2.1. Design of Study

The study is conducted at the Diabetes and Endocrinology Center at Thi-Qar Province, at the period between January to July, (2022). It included (100) cases, (50) healthy control and (50) patients. They divided into two groups as the following:

Group1: Patients group comprised of 50 volunteers from Type 2 Diabetic patients with Diabetic Foot Ulcer (DFU) were collected from Diabetes and Endocrinology Center at Thi-Qar Province.

Group2: Healthy control group comprised of 50 healthy individuals free of T2DM and DFU. They were chosen randomly from the general population; they were visiting AL-Hilal laboratory for checkup.

2.2. Collection of Blood Sample

Three (ml) of venous blood were drawn from all participants by using a disposable syringe, was transferred into gel tube and allowed to clot at room temperature to get serum and centrifuged to separate it at 4000 RPM for 10 min. The serum was transferred into an Eppendorf tube and stored at (-20 °C) until using it to estimate the cytokines (IL₆).

2.3. Determination of Interleukin-6 (IL-6)

Principle of Assay:

ELISA (technique enzyme-linked immune Sorbent adsorptive) kit technique was used to measure serum levels of Interlukine-6. This ELISA kit uses the Sandwich-ELISA principle from the Elabscience company (USA, E-EL- H6156).

2.4. Statistical analysis:

Data were expressed as mean $\pm$ standard deviation (SD) or median (interquintile range). Differences between groups were tested with the student's t-test and non-parametric Chi-square at p. value ≤ 0.05 were considered significant.

3. Results

3.1. The Demographic Characteristics of Patients

Concerning age, about half of the patients 21 (42%) with a range from 60-69 years. The mean age of the two groups were (35.3 ± 14.3) and (58.9 ± 12.1) for control and DFU, respectively, as shown in Table (1). The results of this study showed there was significant differences ($P < 0.001$), among the studied groups. In the current study, all of the DFU patients were older than 41 years.

Fifty patients' group, 40-80 years, were included in this study, as shown in Table (1). Of them, 39 (78%) were male and 11 (22%) were female in patients. Fifty healthy control group 29 (58%) were male, and 21 (42%) were female in control. There was significance different ($P \leq 0.05$) among of the studied groups.

Table (1): Comparing the Mean Age of the Two Studied Groups

Case	Mean $\pm$ SD	P value
Healthy control	35.3 ± 14.3	<0.001*
DFU	58.9 ± 12.1	

* Significant association

Table (2): Demographic Data of the Patients and Healthy controls Involved in the Study

Characteristics	Frequencies (%)	
Case:		
DFU	50 (50%)	
Healthy control	50 (50%)	
Age:		
< 40 years	35 (35%)	CalX ² = 17.7 TabX ² = 9.49 P. value 0.001
40-49 years	16 (16%)	
50-59 years	17 (17%)	
60-69 years	22 (22%)	
70-80 years	10 (10%)	

Sex:		
Male	68 (68%)	CalX ² = 12.96
Female	32 (32%)	TabX ² = 3.84
		P. value 0.000

3.2. Interleukin-6 (IL-6)

The current study showed an increase in the level of (IL-6) in patients with diabetic foot with Mean $\pm$ SD (6.16 $\pm$ 5.24) pg/ml compared with the healthy control group (5.42 $\pm$ 7.74) pg/ml with a significant difference with a statistically significant high ($P \leq 0.05$). As shown in Table (3).

Table (3): Comparison of the levels of IL-6 among two studied groups

Inflammatory Marker	Groups	No	Mean $\pm$ SD	P. value
IL-6 (pg/ml)	Patients	50	6.16 $\pm$ 5.24	0.014*
	Healthy control	50	5.42 $\pm$ 7.74	

* Significant association

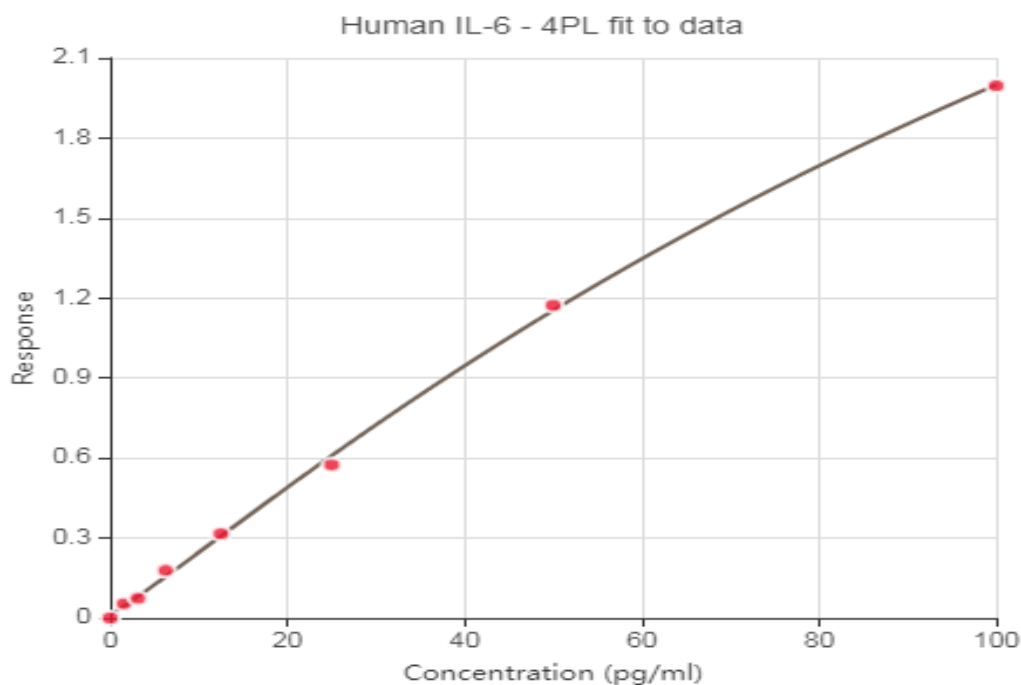


Figure (1): Standard Curve of IL-6.

4. Discussion

Diabetic foot ulcer DFU is a major complication of diabetes mellitus. Diabetes mellitus is a metabolic condition characterized by hyperglycemia arising from impaired insulin production and/or resistance to insulin. There's an increased chance of foot ulceration due to neuropathy and/or Peripheral vascular disease when the diabetic foot is exposed to trauma [8].

The current study had shown that DFU disease was most common in age >60 years (42%) followed in age groups 50-59 years (24%), as shown in Table (2). The result showed there was significance difference among the groups. Several previous studies documented that maximum number of DFU patients occur within age range 40-60 years, Kadhimi, 2021[2] Ali, 2022; SALEH and HADI, 2019; ANYIM *et al.*, 2019 [9,10,11]. Ali, 2022 [9] obtained that DM-foot ulcer is more common in older age groups particularly those above 60 years of age. Age is associated with presence of risk of DM- foot ulcer because increasing age linear with increasing risk of neuropathy and angiopathy the common etiopathology of DFU.

Patients with DFU from both sexes may differ the way to handle the disease and the way they adhere to the care necessary to keep the disease under control. Men in particular, are care less about their feet. The results of the current study were in agreement with results of Ali, 2022 [9]. The result showed there was significance difference among the patients, they observed that male more frequency than female 78% vs 22%, as shown in Table (2). While Kadhimi, 2021; QADIR *et al.*, 2020 [2],[12] contrasted with present results showed there was no significance different between male and female in studied groups. Male predominance in DFU could be linked to factors such as sex-related differences in life styles and professional roles that require the feet to tolerate more pressure. Increased level of outdoor work and poor compliance to foot care practices [13].

The Table (3) were showed an increase in the level of (IL-6) in patients with diabetic foot with Mean $\pm$ SD (6.16 $\pm$ 5.24) pg/ml compared with the healthy control group (5.42 $\pm$ 7.74) pg/ml with a significant difference with a statistically significant high ($P \leq 0.01$). The results of the current study were confirmed the high level of interleukin-6 (IL-6) in the serum of patients with diabetic foot, and this occurs as a result of the increase in the inflammatory process that leads to the response of the immune system and the activation of immune cells. This study agreed with Lanys *et al.*, 2021 [14], who explained in his study that diabetic foot disease is associated with high levels of interleukin-6 in the blood of people with this disease.

The secondary outcome to assess how inflammatory mediators differ among people with diabetes with DFU compared to healthy control, were found to be significantly different between groups. IL-6, were found to be higher in people with diabetes with DFU. This study agreed with Korkmaz *et al.*, 2018 [7].

Conclusions

The current study revealed, that the significantly high IL-6 in diabetic patients with foot ulcer may be fundamental in the development of the ulcer.

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