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Assessment of IL_6 and IL_34 Serum in Patients with Diabetic Foot Ulcers

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ABSTRACT

Diabetes foot ulcers (DFUs) are serious vascular pathological effects related to diabetes mellitus. Interleukins are a subclass of cytokines represent a diverse category of signaling particles which adjust cellular activities. Interleukin-6 (IL-6), a central cytokine in acute inflammatory reaction, stimulating liver to produce acute phase proteins and contributing to the progress of diabetes. Recently, recognized pro-inflammatory cytokine interleukin-34 (IL)-34 binds to colony stimulating factor-1(CSF-1) receptor and is implicated in pathogenesis of different chronic inflammatory and autoimmune conditions. This study aimed to estimate serum concentrations of IL-6 and IL-34 in diabetic individuals with DFUs compared to healthy controls. The research, conducted from January to July 2022 at Al-Hussein Teaching Hospital in Samawa/Iraq, Medical city/Baghdad Hospital in Baghdad/ Iraq. The study was conducted on two groups: 140 DFUs patients and 70 control group. The age range of DFUs patients was 29–87 years, whereas of control group was 18–57 years. The levels of serum IL-6 and IL-34 were evaluation using sandwich ELISA technique. The average random blood sugar level in patients was 226.9 mg/dL. The findings shown that DFUs were significantly associated with factors (P value < 0.05) were: 93(66.4%) are male, high 79(56.40%) are within (31-60) year, smoking 50 (35.7%), overweight 55 (39.3%), type 2 DM 131(93.6%). Similarly, results revealed a significant elevation in IL-6 and IL-34 levels in DEUs individuals compared to control group (P ≤ 0.05).

Keywords- Diabetic foot ulcers; IL_6; IL_34; Demographic data and Sandwich ELISA.

I. INTRODUCTION

Diabetic foot ulcer (DFU) is foot ulceration in a diabetic patient resulting from neuropathy and peripheral vascular disease affecting lower limbs. The classic triads of DFU include ischemia, neuropathy, and infection (Hussein and Saleh, 2024). Infection and delayed wound curative are common in individuals with diabetes as a result of their impaired metabolic functions. Some factors contribute to DFU progress, including diminished cellular responses, reduced peripheral circulation, and decreased local angiogenesis. These complications can lead to peripheral nerves damage, vascular disease, ulcers, deformities, and gangrene (Syafril, 2018). The ulcers are ranging from superficial wounds—defined as full thickness lesions don't penetrate any structure deeper than the dermis—to deep lesions that penetrates deeper structures (fascia, muscle, and bone) (Monteiro-Soares *et al*., 2020).

Diabetic mellitus (DM) represents a set of metabolic conditions recognized by increased blood sugar (Mohammed and Salloom, 2021). It is an important global health challenge in 21st century, and consider fifth major reason of mortality in advanced nations (Khalil, 2016).

The immune systems of patients with DM are typically weakened, making foot infections are life-threatening conditions. Hyperglycemia contributes to increased synthesis of proinflammatory cytokines and damage functions of polymorphonuclear cells including chemotaxis, adhesion, phagocytosis, and intracellular killing. Moreover, weakened leukocyte efficiency, an inappropriate inflammatory reaction, and dysfunction of cellular immune response (Al-Attaby and

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Al-Lami, 2019). Uncontrolled diabetes significantly diminishes leukocyte phagocytic activity, and progresses in microbiocidal rates are associated with hyperglycemia. Elevated metalloproteinases, declined chemotaxis of growth factors and cytokines impede regular wound remedial by extending inflammatory duration (Al-Musawi *et al*., 2021; Stojkov *et al*., 2022).

Cytokines are small and biologically active proteins which adjust cellular evolution, function, differentiation, inflammation and immune responses (Baqer *et al*., 2022). Insulin resistance (IR) is associated with raised levels of TNF-α and IL-6, along with less levels of IL-4 and IL-10. T2DM is now recognized as a chronic inflammatory condition, while T1DM known as a T-helper autoimmune illness (Melekoglu *et al*., 2019; Nussrat and Ad'hiah, 2023). IL-6 is pro- and anti-inflammatory cytokine synthesized from macrophages and T cells that involved in immune defense (Tahir *et al*., 2022). The significant origin of IL-6 is visceral adipose tissue and it a critical player in inflammatory response by motivates the secretion of acute phase proteins from liver, and development of neutrophils construction in bone marrow and B cells production (Akbari and Hassan-Zadeh, 2018). IL-34 is known to associated with diversity of inflammatory, autoimmune disorders, and a probable treatment target. Furthermore, IL-34 is also produced in adipose tissues, where higher levels are highly linked with insulin resistance, particularly in obese individuals (Li *et al*., 2018).

II. METHODOLOGY

2.1 Location

The extant cross-sectional study was carried out in 2022 at Al-Hussein Teaching Hospital in Al muthanna/Iraq, Baghdad Medical City in Baghdad/Iraq. This study was established approval from ethics committees of the participating hospitals.

2.2 Specimens Collection

The present study was involved 140 patients suffering diabetic foot ulcers. Age (29-87 years) and 70 healthy controls of both sexes. For each participant, 3ml of blood was collected and placed in gel tubes for serum separation. The serum specimens were stored at −80° C for immunological examination to evaluate serum of IL-6 and IL-34 using sandwich ELISA Kit, following the manufacturer's guidelines (Elabscience, USA).

2.3 Gathering and Classification of Data

Demographic and clinical data obtained included: sex, age, and smoking, Body mass index (BMI), diabetes type, duration of DM, blood sugar levels, diabetic foot grade, ulcer duration, type and therapy (oral anti-diabetics, insulin, combination therapy, or no get any treatment). Type of DM was determined according to typical criteria established by World Health Organization (WHO) (Malta *et al*., 2019). Random blood glucose levels were also examined.

2.4 Interleukins Assays

Blood specimens allowed to stand for 30–60 minutes, then centrifugation at 4000 rpm for 10 minutes. Resulting serum was reserved at −80 °C until being used. Serum IL-6 and IL-34 concentrations were determined by IL-6 and IL-34 ELISA kits (Elabscience, USA). Findings were expressed as pg/mL.

III. STATISTICAL ANALYSIS

Data analysis was achieved by Excel and SPSS, version 22 (2010). Results were presented as Mean±SD. The variations in IL-6 and IL-34 levels were evaluated using one-way ANOVA, independent t-tests, and LSD tests. Chi-square tests were used for categorical data. For associate the relationships among the calculated parameters, Pearson's correlation coefficient was applied. A significance level of 5% ($P < 0.05$) was employed (McDonald, 2014).

Ethics Approval

Written informed consent was obtained from all participants prior to presence in study, and it was reviewed and accepted by relevant ethics committees.

IV. RESULTS

A. Demographic and Clinical Data

The distribution of DFUs patients in existing study based on age groups as follows: 2 (1.5%) were ≤ 30 year, 79 (56.4%) were 31-60 year, and 59 (42.1%) were ≥ 61 year. Age groups of 31-60 and ≥ 61 were more than ≤ 30 year. A statistically significant variance was identified ($P < 0.05$), showing that occurrence rate of DFUs related positively with age, Table (1). In all tables, * denotes a significant difference at $p < 0.05$.

Table (1): Prevalence of DFUs patients among age groups

Age Groups (years)	No.	Percentage	*P value*
≤ 30	2	1.5%	<0.0001*

31-60	79	56.4%	
≥61	59	42.1%	
Total	140	100%	

This finding of a high occurrence rate with the old ages is comparable to previous that defined about 68% of the affected patients were over 50 year (Fawzy *et al*., 2019). Older age-linked factors like reduced immune response to infection and vascular impairment likely contribute to delay healing outcomes (Musa *et al*., 2018).

Earlier study described positive association among age and DFUs prevalence (Guo *et al*., 2022). Present findings varied with a study which revealed no significant age-linked differences (Huang *et al*., 2019). Differing age identity criteria applied across included studies may be reason of diverse findings. In older adults, delayed wound repair is associated with multiple factors like peripheral arterial disease and weakened immune defenses (Marzoq *et al*., 2019).

The distribution of sex in current study as follows: 93(66%) were male and 47(34%) were female. This result showing a statistically significant relationship ($P < 0.05$) between distribution of DFUs and sex, Table (2).

Table (2): Distribution of DFUs patients among sex groups

Sex	No.	Percentage	*P value*
Female	47	34%	<0.0001*
Male	93	66%	
Total	140	100%	

A Turkish study agreement with our finding, reporting a significant difference of sex factor in DF patients (Korkmaz *et al*., 2018). Similarly, most patients were 42 (56%) male out of 75 their study individuals (Kagwa *et al*., 2018). In contrast, our finding varied from Saudi Arabia research which reported that rate 70% of DFUs individuals were females (Fawzy *et al*., 2019). Additionally, two further studies indicated that sex was unrelated risk factor of DFUs progress, although authors didn't provide any interpretation for this negative outcome, perhaps due to small specimen size (Khalifa, 2018; Yazdanpanah *et al*., 2018).

Consistent with our results and earlier study, DF syndrome appears to be significantly more widespread within males (Seghieri *et al*., 2019). They suggested that females have a lesser risk versus males relatively as a result of less serious neuropathy, improved joint flexibility, and reduced foot pressure) Navarro-Flores and Cauli, 2020).

In our study, 50(36%) of DFUs patients were current smokers, however 90(64%) were non-smokers, Table (3). The result discovered a significant association ($P < 0.05$) among smokers and DFUs. This is similar to the study which reported a statistically significant association among smoking and DFUs (Eltilib, 2021).

Table (3): Rate of DFUs patients among smoking groups

Smoking	No.	Percentage	*P value*
Yes	50	36 %	0.001*
No	90	64 %	
Total	140	100 %	

The our study is also compatible with findings of two studies which identified a significant correlation among smoking and DF incidence (Mariam *et al*., 2017; Zhang et *al*., 2017). Current result differ from Brazil study, which reported not associated between smoking and the risk of DFUs leading to lower extremity amputation and mortality in diabetic people (Costa *et al*., 2017).

Former finding has highlighted smoking as a risk cause of DFUs due to tissue hypoxia, which lead to vascular and neuropathic complications in lower limbs of DM individuals (Zhang et *al*., 2017). Its pathogenesis is limited ability for O_2 transport in blood, caused toxic substances in cigarette and outcomes in tissue O_2 deficiency and arteriospasm. This destruction triggers compensatory erythrocytosis who raises blood viscosity and limits blood flow. Reduction in oxygen delivery inhibits diabetic ulcers healing, giving rise to lower extremities amputation (LEA) (Lee *et al*., 2022).

According to BMI, occurrence of DFUs individuals was as follows: 2(1.5%) were underweight, 41(29%) were normal, 55(39.5%) were overweight and 42(30%) were classified as obese. Findings from the current study revealed that overweight individuals higher values compared to those with normal and underweight. Additional, Obese DM individuals appeared to have a higher likelihood to develop DFUs as compared with DM individuals with normal BMI, Table (4).

Table (4): Rate of DFUs patients among BMI groups

BMI	No.	Percentage	*P value*
Under Weight	2	1.5%	<0.0001*
Normal	41	29%	

Overweight	55	39.5%	
Obesity	42	30%	
Total	140	100%	

A significant variation association (P <0.05) detected in present study demonstrates that the occurrence rate of DF rises with increasing BMI like Ethiopian study (Mariam *et al*., 2017). This may be resulting from high foot pressure utilized by diabetic individuals with higher BMI, as both obesity and overweight can significantly impair intensively normal blood circulation in lower limbs, thus elevating risk of developing DFUs.

Furthermore, a study confirmed that relationship among BMI and DF, and individuals with greater BMI have an increased risk of occurring DF lesions (Sohn *et al*., 2011). Nevertheless, our results contrast with a study who show link among BMI and DFUs, who indicated that there is no statistically significant link among BMI and occurrence of DF ulcers (Guo *et al*., 2022).

Out of study specimens, 9(6.4%) patients presented with T1DM and 131(93.6%) were T2DM. A statistically significant association was detected among DFUs and DM type, Table (5).

Table (5): Rate of DFUs patients among DM type groups

DM Type	No.	Percentage	*P value*
T1DM	9	6.4 %	<0.0001*
T2DM	131	93.6 %	
Total	140	100%	

Like results were which shown T2DM was significantly related with the incidence of DFUs (Mariam *et al*., 2017). Contrasting current result, Hussein *et al*., (2022) reported who type of DM and occurrence of DF ulcers wasn't related.

Conversely, main mechanisms remain unclear. The potential explanation could be in patients of T2DM, there are associated with many complications as structural changes in bones of foot, peripheral neuropathy, and peripheral arterial illness due to atherosclerosis. Thus, the patient may have impair tissue healing, O_2 utilization, nutrient moving, and cellular detoxification causing ulcers formation in extremities (Mariam *et al*., 2017). Likewise, limited data can be shown about DFUs epidemiology in T1DM.

We were employing Wagner's taxonomy in detect DF grades and performed by physicians (Pitocco *et al*., 2019). In recent study, grades of DF ulcers as follows: 35 (25 %) were grade I, 32 (22.8%) were grade II, 25(17.9%) were grade III, 28 (20%) were grade IV and 20(14.3%) were grade V. This result indicates that rate of DF isn't significant difference (P > 0.05) linked with DF grades, as shown in table (6).

Table (6): Rate of DFUs patients among DF grade groups

DF grade	No.	Percentage	*P value*
Grade I	35	25%	0.29
Grade II	32	22.8%	
Grade III	25	17.9%	
Grade IV	28	20%	
Grade V	20	14.3%	
Total	140	100	

A like study found that gradation made no statistically variance to DF ulcers (Musa *et al*., 2018). Different our result, a study described that found a correlation between ulcer thickness and DFUs severity as stately by Wagner's classification (Jalilian *et al*., 2020).

Based on treatment administration, this research revealed 40 (28.6%) were insulin administration, 43 (30.8%) were oral antibiotic administration, 55(39.2%) were receiving both treatments, and 2 (1.4%) were no drug administration. There is significant relation among DFUs and treatment administration (P < 0.05), Table (7).

Table (7): Rate of DFUs patients among treatment administration groups

Treatment using	No.	%	*P value*
Insulin	40	28.6	<0.0001*
Oral antibiotic	43	30.8	
Both	55	39.2	
No drug	2	1.4	
Total	140	100	

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Our result showed that a large percentage of patients 55(39.3%) were administration a combination of insulin and oral antibiotic treatments. This significantly relation among DF ulcers and treatment administration consistent with an Iranian research who reported significant link between drug administration and severity of DFUs. Likewise, similar a study stated a association among both oral medications and insulin injections with DFU degree (Madmoli *et al*., 2019). The present study dislike with Turkish study that reported no significant correlation among insulin drugs, antibiotic treatment and the occurrence of DFUs (Sen *et al*., 2019). While there isn't precise cause of this relationship, reflect that insulin injection is more closely linked to DFUs severity and body's inflammation response (Welty *et al*., 2016; Jalilian *et al*., 2020). Finally, random blood sugar of individuals was 226.9 mg/dL.

B. Immunological Estimations of Plasma Levels of Selected Interleukins

A total of 3ml of blood was gathered from 210 participants, 140 specimens for patients of DFUs and 70 specimens for healthy control group, and placed in gel tube for separation of serum and kept at −80 °C for immunological study. Plasma levels of interleukins were determine by Sandwich ELISA Human IL-34 and IL-6 (Elabscience, USA) and concentrations were manifested in pg/ml. IL-6 and IL-34 levels were planned in both patients and control groups, and revealed statistical variations between study groups, and association among both groups, Table (8).

Table (8): Evaluation of IL- 6 and IL- 34 between patient and control groups.

s	Patient	Control	*P value*
IL- 6	24.6±18.5	11.10±1.41	<0.0001*
IL- 34	556.47±74.44	444.74±165.2	<0.0001*

The findings indicated that levels of IL-6 and IL-34 between patients and control groups plasma is significantly difference ($P < 0.05$). Mean levels of IL-6 and IL-34 were observed to be greater in individuals with DF (24.6± 18.5 pg/ml and 556.47± 74.44 pg/ml, individually) plasma concentrations compared with control (11.10± 1.41 pg/ml and 444.74± 165.2 pg/ml, individually) plasma concentrations in a similar finding of Al-Salih and Ali (2021) which exposed that significant difference rise ($P \leq 0.05$) of IL-6 levels in patients group as comparison with control group resulting from inflammation. Additionally, like studies presented that DM patients and DF ulcers at different levels had greater plasma levels of IL-6 versus DM patients without DF ulcers (Zorena *et al*., 2020).

A vital proinflammatory cytokine is IL-6 that contributes to the pathological mechanisms of DF disorder. Also, IL-6 assists in both inflammatory and autoimmune illnesses (Lee *et al*., 2019). Levels of IL-6 are strongly associated with insulin resistance (IR) in T2DM individuals and its complications (Chandrika, 2022). Research has shown that IL-6 decreases insulin sensitivity. Hence, level of IL-6 serves as an independent predictor future possibilities of increasing T2DM and its related adverse effects (Al-Salih and Ali 2021).

Similar to current result, a prior study reported who IL-34 levels were elevated in T2DM patients compared with control, and effective specific curve evaluation demonstrated which IL-34 has strong specific capacity for risk the DM complications (Zorena *et al*., 2016). Moreover, Chang *et al*., (2014) described IL-34 was a significant positive relationship with IR associated to metabolic variables.

Interleukin-34 enhanced fat buildup and impairs insulin-stimulated glucose transport (Chang *et al*., 2014). It also stimulates monocyte and macrophage differentiation which leads to release of pro-inflammatory cytokines for instance TNF-α and IL-6 (Anegon, 2017). IL-34 is implicated in a variety of autoimmune and inflammatory conditions, and its potential as a new therapeutic target has been recognized. Furthermore, it is detectable in adipose tissues, and significantly upregulated expression in obesity individuals and strongly correlated to IR (Piao *et al*., 2019).

V. CONCLUSION

In brief, our research demonstrated which IL-6 and IL-34 levels were significantly higher in DM individuals with DFUs compared to DM without DFUs. The present study provides strong evidence assistant influence of higher IL-6 and IL-34 in pathogenesis of DF ulceration. Factors found to be associated with DFU involved sex, age, smoking status, and DM type, duration of DM, duration of DFUs and drug administration. In contrast, BMI was observed as a distinct factor in progress of DFUs.

Recommendations

We recommend a larger patient cohort and covering the estimations of additional cytokines particularly IL-12, IL-17, and IL-18 in individuals with diabetic foot ulcers. Furthermore, using both liquid and tissue biopsy for the immunological assessments may contribute more comprehensive insights.

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Conflict of Interest Disclosure

We declare that there are no conflicts of attention concerning this work.

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