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IMMUNOLOGICAL AND METABOLIC BIOMARKERS IN DIABETIC FOOT ULCERS: A COMPARATIVE CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Diabetic foot ulcers (DFUs) are among the most disabling and expensive complications of diabetes mellitus, which occur as a result of a combination of metabolic dysfunction, vascular dysfunction, and immune dysregulation. Although increased awareness has been reported, the immunological processes that distinguish between patients with and without active ulceration are yet to be fully described. **Objective:** The purpose of the study was to compare and assess the glycemic indices, lipid profiles, and a group of inflammatory and immunological biomarkers interleukin-18 (IL-18), tumor necrosis factor-beta (TNF- beta), interleukin-10 (IL-10), basic fibroblast growth factor (BFGF), and C- reactive protein (CRP) across three well-defined clinical groups. **Methods:** The study adopted a comparative cross-sectional design and included 150 participants, who were stratified as **follows:** patients with confirmed DFU (n=50), diabetic patients without foot ulcers (n=50) and age and sex matched healthy controls (n=50). The results of the biochemical and immunological measurement were taken on the basis of fasting venous blood samples and the analysis of them with the help of standardized measurements. **Results:** DFU patients exhibited markedly elevated fasting glucose (192±35 mg/dL) and HbA1c (9.1±1.2%) relative to healthy controls (P<0.001). Dyslipidemia, evidenced by elevated total cholesterol, triglycerides, and low-density lipoprotein (LDL), was observed across both diabetic groups. Pro-inflammatory markers CRP (12.5±4.3 mg/L), IL-18 (340±55 pg/mL), and TNF-β (58±12 pg/mL) were significantly higher in DFU patients than in both comparator groups (P<0.001). Concurrently, IL-10 and BFGF levels were elevated in DFU patients, suggesting a compensatory anti-inflammatory response. **Conclusion:** DFU is a two-fold immunological burden of increased pro-inflammatory signaling and impaired reparative response. Incorporation of inflammatory biomarkers with glycemic monitoring on a regular basis can lead to a more targeted therapeutic treatment of diabetic foot complications and risk stratification earlier.

KEYWORDS: diabetic foot ulcers; inflammatory cytokines; glycemic control; wound healing biomarkers; immune dysregulation.

INTRODUCTION

Diabetes mellitus is ranked among the major global health crises of the twenty-first century, and the rate of prevalence is ever increasing in both wealthy and impoverished nations. According to the International Diabetes Federation, over 537 million adults now live with diabetes in the world with the figure expected to rise over 780 million by 2045.[1] Diabetic foot ulcers (DFUs) among the long-term complications of this condition take a very specific place in the hierarchy of morbidity, healthcare use, and socioeconomic strain. DFU is estimated to occur in 1525 percent of diabetic persons globally throughout their lives, and is the most common trigger of non-traumatic amputation of lower extremities.[2]

DFU pathogenesis is multifactorial in nature, and it is a result of the interaction between peripheral neuropathy, vascular insufficiency, and a chronically dysregulated immune environment. Chronic hyperglycemia worsens leukocyte chemotaxis, phagocytic ability, and T-cell cell mediated responses as well as enhancing accumulation of

advanced glycation end-products (AGE) which further undermine vascular endothelial stability.[3] The ensuing tissue perfusion and cellular immunity impairment creates a wound microenvironment, which is ill-prepared to carry out the canonical stages of healing hemostasis, inflammation, proliferation, and remodelling.[4]

The development and chronicity of DFU has been highlighted as highly dependent on particular immunological mediators. The local tissue destruction along with the blockage of angiogenesis is maintained by pro-inflammatory cytokines, including interleukin-18 (IL-18) and tumor necrosis factor-beta (TNF-β) whereas the systemic responses like C-reactive protein (CRP) indicate the chronic low-grade of inflammation, which is typical of poorly controlled diabetes.[5,6] On the other hand, anti-inflammatory cytokines like interleukin-10 (IL-10) and angiogenic factors like basic fibroblast growth factor (BFGF) are also endogenous repair cues that are often overstimulated or misregulated in the chronic wound environment.[7]

Glycemic control, which is measured by the hemoglobin A1c (HbA1c), is a composite measure of metabolic regulation and is intrinsically associated with vascular and immune competence. The co-occurrence of dyslipidemia with hyperglycemia further exacerbates peripheral arterial disease and tissue ischemia as well, posing compounding barriers to wound resolution.[8] Nonetheless, with all these established pathological factors, the simultaneous examination of metabolic indices and a wide immunological panel in well-stratified clinical groups is not well studied, especially in the Iraqi and regional Middle Eastern environment.[9]

The current research thus attempted to describe and contrast glycemic status, lipid profile parameters, and a specific group of immunological biomarkers IL-18, TNF-b, IL-10, BFGF, and CRP between patients with active DFU, diabetic individuals without ulcers, and healthy controls. This study aims at revealing biomarker signatures that can be used to aid risk stratification, early clinical diagnosis, and inform the development of adjunctive immunologically-targeted therapies by elucidating the immunometabolic landscape of DFU.[10,11]

MATERIALS AND METHODS

Design and Setting of the Study

This research design used a comparative cross-sectional research carried out in selected facilities of diabetes care in Baghdad, Iraq. The enrollment of participants was planned to be conducted in the period between September 2025 and February 2026. The institutional review board granted us ethical approval in accordance with the declaration of Helsinki. All the participants were informed and provided written informed consent before being enrolled in the study and no personal and clinical data was disclosed in the course of the study. The participants were free to drop out at any time.

Participants

One hundred and fifty participants were recruited and divided into three equal groups (DFU group: including 50 patients with clinically confirmed DFU; diabetic control group: including 50 patients with established type 1 or type 2 diabetes mellitus but without active foot ulcers; and healthy controls: including 50 healthy individuals matched according to age and sex). Diabetes mellitus was diagnosed using the American Diabetes Association (ADA) 2024 Standards of Medical Care.[12] The sample size was enough to include eligible diabetic patients aged 18 years and above with a documented diagnosis according to ADA criteria. All diabetic participants were excluded with uniform criteria, that is, severe non-diabetic systemic comorbidities (e.g. active malignancy, dialysis-dependent chronic kidney disease), current immunosuppressive therapy, acute infectious illness within 2 weeks of sample collection, and pregnancy or lactation. Healthy controls were also obligated to be free of metabolic, autoimmune, and acute infectious disease history before enrollment.

Clinical and Demographic Data Gathering

All participants were filled in standardized case report forms, and the following information was recorded: age, sex, smoking status, hypertension, duration of diabetes, and current pharmacological therapy, including the use of insulin. In DFU patients, further ulcer-specific information was recorded, including anatomical site (toes, sole, or heel), ulcer duration (stratified into less than 4 weeks, 4-12 weeks, or greater than 12 weeks), and the presence of local edema, and ulcer classification (neuropathic, ischemic or mixed etiology).

Biological Collection and Processing of Samples

Venous blood samples (5 mL) were taken out of the antecubital vein under aseptic conditions after at least eight hours of overnight fasting. The samples were split into two aliquots: serum (centrifuged at 3,000 rpm during 10 minutes) that will be used in biochemical and immunological tests, and whole blood to perform HbA1c. Serum samples were aliquoted in capped cryotubes and frozen at -80C until batch testing to ensure that freeze-thaw error was minimized.

Biochemical and Immunological Tests

Glycemic conditions were evaluated through the fasting plasma glucose with a standardized enzymatic colorimetric technique and HBA1c through an automated analyzer with the principle of high-performance liquid chromatography (HPLC). Lipid profile of total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were determined by appropriate colorimetric assays on a semi-automated biochemistry analyzer. CRP was measured using the immunoturbidimetry. Commercially validated enzyme-linked immunosorbent assay (ELISA) kits were used to determine serum concentrations of IL-

18, TNF-b, IL-10, and BFGF in each case, and all samples were analyzed in duplicate to ensure reproducibility.

Statistical Analysis

The analyses of the data were conducted with the help of IBM SPSS Statistics 26.0. Continuous variables that follow a normal distribution (tested with the help of the Shapiro-Wilk test) were presented in terms of mean, standard deviation (SD), and compared between the groups by one-way analysis of variance (ANOVA) with the Tukey honest significant difference (HSD) post hoc test. The Kruskal-Wallis test and Mann-Whitney U test were used to analyze the non-normally distributed continuous variables with a post hoc test. Frequencies and percentages were used to present the categorical variables and to compare them with each other by the Chi-square test offered by Pearson. Pearson's or Spearman's correlation coefficient was used to assess relationships between selected continuous variables. All analyses were set at statistical significance, $P<0.05$.

RESULTS

Demographic and Clinical Characteristics

The age distribution was similar in the three study groups with mean ages of 57.3±8.9, 55.6±9.2, and 56.1±7.8 years in the DFU, diabetic control and healthy control groups, respectively (P=0.158). On the same note, there was no significant difference in smoking prevalence and hypertension between groups (P=0.478 and P=0.842, respectively). A statistically significant male bias was, however, detected in the DFU group (72% male), which was more balanced in the other two groups (P=0.001). The use of insulin therapy was also much higher in DFU patients (56%) compared to diabetic controls (36) (P=0.015). **Table 1** shows these findings.

Table 1: Demographic and Clinical Features of the Study Population

Parameter	DFU Patients (n=50)	Diabetic Controls (n=50)	Healthy Controls (n=50)	P-value
Age (years, mean±SD)	57.3±8.9	55.6±9.2	56.1±7.8	0.158
Age <50 years, n (%)	12 (24%)	14 (28%)	13 (26%)	0.132
Age 50–60 years, n (%)	20 (40%)	22 (44%)	21 (42%)	
Age >60 years, n (%)	18 (36%)	14 (28%)	16 (32%)	
Sex, male/female	36/14	26/24	27/23	**0.001***
Smoking, yes/no	18/32	15/35	16/34	0.478
Hypertension, yes/no	22/28	20/30	21/29	0.842
Insulin therapy, yes/no	28/22	18/32	—	**0.015***

Note. *Statistically significant (P<0.05). DFU: diabetic foot ulcer; SD: standard deviation.

Ulcer Characteristics

The most frequent site of ulcers among 50 patients with DFU was the plantar surface (sole) (44%), then toes (36%), and heel (20%). Most of the ulcers were 4-12 weeks (56%), and 24% were shorter, and 20% more than 12 weeks. Local edema was also exhibited in 60 percent of DFU patients. The distribution of ulcer types varied significantly among the types of ulcers (P=0.025), with the majority being neuropathic (40%), then the proportion of both ischemic and mixed-types ulcers were equal (30% each), as detailed in **Table 2.**

Table 2: Clinical Characteristics of Diabetic Foot Ulcers (n=50)

Parameter	n	%	P-value
Ulcer location			0.234
– Toes	18	36%	
– Sole	22	44%	
– Heel	10	20%	
Ulcer duration			0.312
– <4 weeks	12	24%	
– 4–12 weeks	28	56%	
– >12 weeks	10	20%	
Swelling present	30	60%	0.458
Ulcer type			**0.025***
– Neuropathic	20	40%	
– Ischemic	15	30%	
– Mixed	15	30%	

Note. *Statistically significant difference in ulcer type distribution (P<0.05).

Glycemic Indices and Lipid Profile

The fasting glucose and HbA1c levels between both diabetic groups were significantly higher compared to the healthy controls (P<0.001). DFU patients reported the greatest mean fasting glucose (192±35 mg/dL) and HbA1c (9.1±1.2%) which highlights the correlation between long-term hyperglycemia and vulnerability to ulcers. Concerning the lipid profile, total cholesterol, triglycerides, and LDL were all considerably higher in diabetic subjects than in controls (P<0.05), whereas differences in HDL were not significant (P=0.053). The summary of these parameters is given in **Table 3. Figure 1** also shows how HbA1c levels are distributed and intergroup varied.

Table 3: Glycemic Indices and Lipid Profile Parameters across Study Groups

Parameter	DFU Patients (n=50)	Diabetic Controls (n=50)	Healthy Controls (n=50)	P-value
Fasting glucose (mg/dL)	192±35	185±28	92±12	**<0.001***
HbA1c (%)	9.1±1.2	8.8±1.0	5.3±0.4	**<0.001***
Total cholesterol (mg/dL)	212±32	208±28	182±22	**0.014***
Triglycerides (mg/dL)	180±45	170±40	120±28	**0.009***
LDL (mg/dL)	135±28	130±25	95±20	**0.012***
HDL (mg/dL)	38±6	40±7	52±8	0.053

Note. *Statistically significant (P<0.05). DFU: diabetic foot ulcer; HbA1c: glycated hemoglobin; LDL: low-density lipoprotein; HDL: high-density lipoprotein; SD: standard deviation.

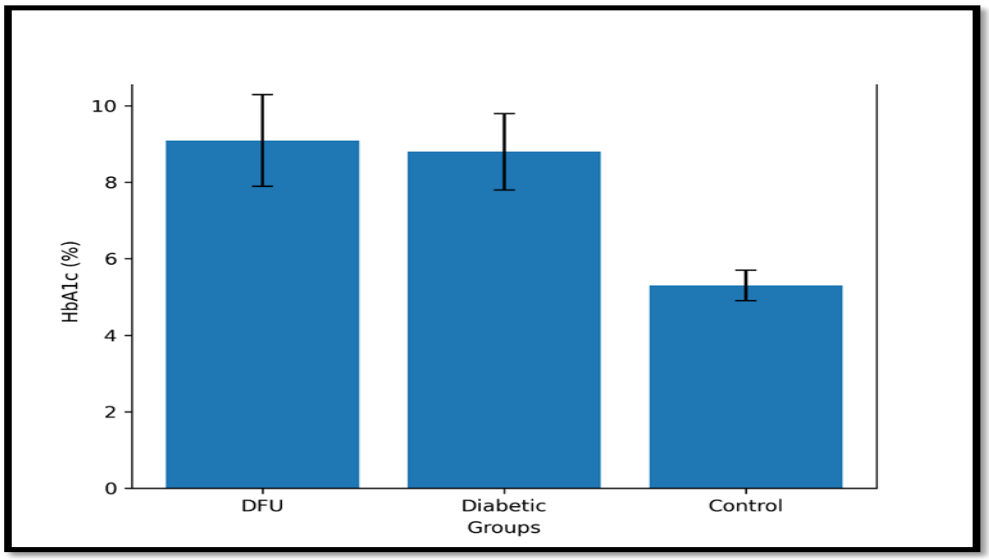

Figure 1: Comparison of mean HbA1c levels (±SD) among DFU patients, diabetic patients without ulcer, and healthy controls.

Inflammatory and Immunological Biomarkers

The intergroup differences were statistically significant (P<0.001 in the case of IL-18, TNF-b, IL-10, and BFGF; P<0.05 in the case of CRP) in all five immunological markers. DFU patients showed the strongest increases with CRP of 12.5±4.3 mg/L, IL-18 of 340±55 pg/mL, and TNF-b of 58±12 pg/mL, all of which were significantly greater than the comparator groups. It is worth noting that anti-inflammatory IL-10 (32±8 pg/mL) and angiogenic BFGF (18±5 pg/mL) both significantly increased in DFU patients compared to healthy controls, yet the presence of ulceration in the patients indicates that these countermeasures were not sufficient to counter the pro-inflammatory environment. The full data of biomarkers are shown in **Table 4. Figure 2** shows the pairwise correlation of the main immunological and glycemic biomarkers.

Table 4: Inflammatory and Immunological Biomarkers across Study Groups.

Biomarker	DFU Patients (n=50)	Diabetic Controls (n=50)	Healthy Controls (n=50)	P-value
CRP (mg/L)	12.5±4.3	8.7±3.2	2.1±0.9	**<0.05***
IL-18 (pg/mL)	340±55	210±40	105±25	**<0.001***
TNF-β (pg/mL)	58±12	40±10	15±5	**<0.001***
IL-10 (pg/mL)	32±8	28±7	12±4	**<0.001***
BFGF (pg/mL)	18±5	15±4	6±2	**<0.001***

Note. *Statistically significant. CRP: C-reactive protein; IL-18: interleukin-18; TNF-β: tumor necrosis factor-beta; IL-10: interleukin-10; BFGF: basic fibroblast growth factor; SD: standard deviation.

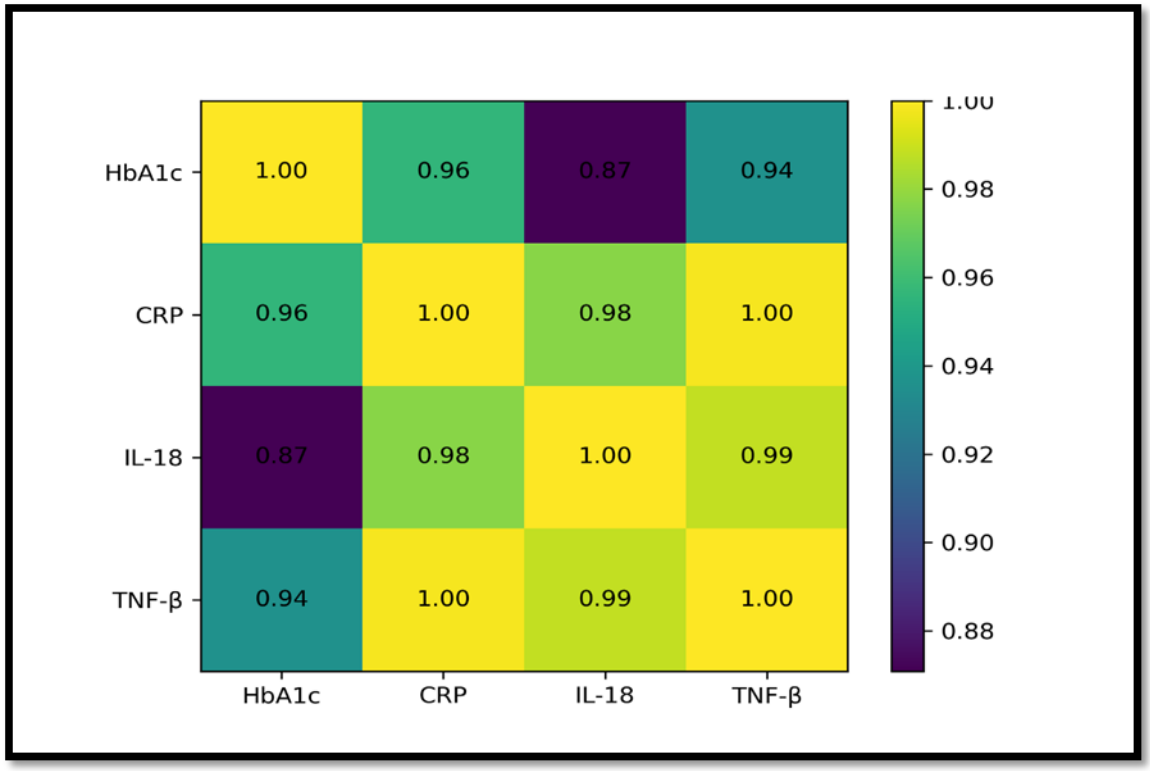

Figure 2: Heatmap correlation matrix demonstrating pairwise relationships between HbA1c, CRP, IL-18, and TNF-β concentrations across the combined study cohort.

DISCUSSION

The current research gives an in-depth immunometabolic profile of patients with diabetic foot ulcers in relation to diabetic patients with no ulcer and healthy controls. The overall results support a DFU pathogenesis model that is mediated by the interplay of persistent hyperglycemia, atherogenic dyslipidemia, and chronic activation of an inflammatory immune axis.

The fact that there were no major differences in age between groups is consistent with previous cohort studies that age although a proven modulator of immune competence is not a determinant of ulcer development in well-established diabetic cohorts.[13,14] Conversely, the high male pre-eminence in DFU group (72) also reflects the findings of a number of regional and global registries. These sex inequities have been explained by the occupational exposure, reduced compliance to foot care practices, and delayed healthcare-seeking behavior in male patients.[15] The much higher percentage of DFU patients using insulin therapy (56% vs. 36%, P=0.015) is probably due to more severe disease and longer duration of the disease in this group as opposed to a causal association with ulceration itself.[16]

The glycemic data confirm the well-established relationship between chronic hyperglycemia and diabetic foot complications. DFU patients had a mean HbA1c of 9.1±1.2%, showing poor long-term glycemic control. Prolonged hyperglycemia promotes the generation of end-products of advanced glycation (AGEs) and reactive oxygen species which all worsen the activity of neutrophils, endothelial stability, and angiogenic potential.[17] The convergence of these mechanistic pathways results in the pro-ulcerative tissue microenvironment that was clinically observed in our DFU cohort. The fact that the HbA1c and IL-18 concentration are positively related gives further data about the fact that glycemic burden is directly related to the level of inflammatory activation.[18]

Dyslipidemia, partially supported by the importance of notable changes in the total cholesterol, triglycerides, and LDL in both groups of diabetics, is a known cause of peripheral arterial disease and poor tissue perfusion. Increased LDL facilitates the development of foam cells and atherosclerotic plaque, therefore, decreasing the microvascular circulation necessary to wound oxygenate and to repair cells.[19] Although the difference in the HDL was not statistically significant (P=0.053), the HDL levels in diabetic patients were consistently lower and the literature revealed that in diabetic patients the reverse cholesterol transportation capacity decreased.[20]

The most educative clinical findings of the current study may be associated with the immunological biomarker panel. CRP, IL-18 and TNF- B were significantly and strongly increased in DFU patients compared to the two comparators. The IL-18, which is a part of the IL-1 superfamily of cytokines, stimulates interferon-gamma synthesis, enhances macrophage-induced oxidative stress and inhibits keratinocyte migration all of which together halt wound healing.[21] The strong IL-18 increase (340±55 vs. 105±25 pg/mL in controls) confirms the

previous studies that found IL-18 as a predictor of DFU severity and independent predictor of the occurrence of ulcers.[22] Equally, TNF-B (lymphotoxin-alpha) maintains tissue catabolism and inhibits fibroblast growth, which also promotes the degradative wound environment.[23]

Of special interest is the simultaneous increase of anti-inflammatory IL-10 and angiogenic BFGF in DFU patients. These results are in line with the idea of a reparative response, which is compensatory, yet inadequate. Regulatory T-cells and alternatively activated macrophages produce IL-10 and are trying to oppose the pro-inflammatory cascade.[24] Likewise, BFGF enhances proliferation of fibroblasts and neovascularization that is also an endogenous effort to reestablish tissue integrity.[25] The fact that the ulceration persists notwithstanding the high concentration of these reparative cues implies dysfunction or stoichiometric insufficiency, i.e. the strength of the pro-inflammatory impetus is greater than the ability of these counter-regulatory processes. This reading can be justified by studies that reveal that reparative growth factor receptors themselves can be suppressed in hyperglycemic and oxidative environment in chronic wounds.[25]

The combination of the immunological and metabolic phenotype of DFU patients in the study is a self-perpetuating pathophysiological loop: hyperglycemia results in the production of inflammatory cytokines, which increases oxidative stress and endothelial dysfunction, which further worsen tissue perfusion and immune activity. This cascade conditions the situation when even the up-regulated compensatory signals such as IL-10, BFGF, are made inadequate. The clinical heatmap (Figure 2) of the strong inter-correlations between CRP, IL-18, and TNF-B supports the presence of a coordinated inflammatory network instead of isolated elevation of the biomarkers.[21,22]

These results have a clinical implication. Routine inclusion of IL-18, TNF-b, and CRP in diabetic foot risk evaluation can improve the early detection of individuals at risk of ulcer or development especially when used with conventional HbA1c checks. Pharmacological approaches that inhibit inflammatory processes by selective cytokine antagonism or immunomodulatory adjuncts to standard wound therapy are a rationally-based future treatment option.

Strengths and Limitations

Such features as the three-group comparative design, simultaneous assessment of metabolic and immunological parameters, and the use of standardized assay protocols, support the study. However, the cross sectional design does not allow causal inference and the sample size (relatively small) does not allow statistical power to do subgroup analyses. There were no longitudinal follow-up data to determine the trends of biomarkers in regard to ulcer healing or the amputation outcomes. Moreover, possible confounders (statin treatment, wound infection, ulcer grade (Wagner classification), and duration of diabetes) were not completely controlled, and this could be a factor in the biomarker profiles reported.

CONCLUSION

This cross-sectional comparative study shows that diabetic foot ulcers are a unique and clinically relevant immunometabolic phenotype. DFU patients have higher levels of hyperglycemia and dyslipidemia than diabetic patients without ulcers, as well as significantly increased pro-inflammatory signaling in the form of increased CRP, IL-18, and TNF-b. The simultaneous increase in anti-inflammatory IL-10 and angiogenic BFGF reflects the existence of an active, but insufficient, counter-regulatory reaction. Taken together, these results favor the idea of DFU as a multifactorial, immunoinflammatory disease that cannot be just reduced to metabolic dysregulation. The combination of inflammatory biomarkers with glycemic monitoring has potentials of enhancing the risk stratification, early diagnosis, and the creation of specific therapeutic interventions to the complications of diabetic foot.

Data Availability: Available from the corresponding author upon reasonable request.

Conflicts of Interest: **None.**

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