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**Original Research Article**

# Dysregulation of immunoglobulins and complement proteins in diabetic foot infections

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## ABSTRACT

**Background:** Diabetic foot infections (DFIs) continue to be a substantial contributor to morbidity, disability, and limb loss in resource-limited nations. Hyperglycemia is associated with impaired wound healing; however, the relationship between immune dysregulation and metabolic glitches in diabetic foot infections remains imperfectly characterized.
**Methods:** This cross-sectional analytical investigation recruited 55 patients with diabetic foot infections from a specialist diabetes care center in Eastern Sudan (2024–2025). Clinical factors, ulcer intensity (SINBAD score), fasting blood sugar (FBS), and glycated hemoglobin (HbA1c) were recorded. Plasma immunoglobulins (IgA, IgG, IgM) and complement (C3,C4) levels were measured and compared with reference values. Associations among immunological markers, glycemic indices, and ulcer intensity were analyzed using chi-square tests, correlation analyses, and regression models.
**Results:** The study consisted of 60% males and 40% females, with a mean age of 50.4±16.0 years and an average diabetes duration of 10.3±6.9 years. The majority exhibited advanced ulceration, with 52.7% receiving a SINBAD score of 6. The mean FBS and HbA1c levels were 191.0±71.9 mg/dl and 9.12±2.25%, respectively. Relative to reference values, IgA, C3, and C4 exhibited elevation (P<0.001), whereas IgM was reduced (P<0.001). Low IgM showed a linkage with increased HbA1c (P=0.030), whereas C3 was linked to FBS (P=0.049).
**Conclusions:** DFIs in Sudanese patients are accompanied by immune dysregulation, reduced IgM, and persistent complement signaling, linked to hyperglycemia. Assessing immunological markers alongside glycemic indices may expand the practical utility of prognostic evaluation in resource-limited settings.

**Keywords:** Diabetic foot infection, Immunoglobulin, Complement, HbA1c, Fasting blood sugar, Sudan

## INTRODUCTION

Diabetic foot infections (DFIs) stand as a vicious consequence of diabetes since they bring prolonged ulcers that need extended hospital treatment and contribute to massive amputations. The worldwide prevalence of diabetic foot ulcers affects 25% of diabetic adults who will develop foot ulcers during their lifetime, and most cases of limb amputation result from infections, which highlights the requirement for international cooperation to combat this problem.[1] This is accentuated by poor access to specialized wound care and delayed medical treatment. This cannot be overstated: suboptimal glycemic control, particularly in low- and middle-income countries, including Sudan, significantly exacerbates the DFI problem, underscoring the importance of improved diabetes care.[2] The underlying cause of DFIs is multifaceted, involving neuropathy, ischemia, compromised wound healing, and immunological dysfunction.[3] Hyperglycemia not only promotes vascular impairment but also directly undermines host defensive mechanisms, involving neutrophil chemotaxis, macrophage activity, and antibody function. Research has thoroughly documented cellular immunological

deficiencies in diabetes, yet the exact function of humoral immunity through immunoglobulin and complement pathways in diabetic foot infection progression remains unclear.[4] The body depends on immunoglobulin M (IgM) to activate complement frameworks and fight bacterial infections. Conversely, Immunoglobulin A (IgA) and Immunoglobulin G (IgG) facilitate adaptive and mucosal immunity, whereas complement proteins (C3 and C4) facilitate pathogen opsonization and injury. The dysregulation of these variables may consequently be associated with persistent hyperglycemia, increased risk of infection, and compromised ulcer healing.[5,6]

From a hematologic standpoint, immunoglobulins and complement proteins are fundamental elements of humoral immunity and systemic inflammatory control. Complement proteins C3 and C4 are essential mediators of the classical and alternative pathways, significantly contributing to opsonization, immune complex clearance, and the amplification of inflammatory cascades.[7] Ongoing complement activation has been associated with chronic inflammatory and metabolic diseases, leading to endothelial dysfunction and compromised tissue repair.[3-7]

Additionally, IgM functions as the principal antibody in the initial immunological response and in effective complement activation. Deficiency or functional impairment of IgM in chronic inflammatory conditions may indicate reduced humoral immunological competence and decreased pathogen clearance. In diabetes, prolonged immunological activation and metabolic imbalance may modify immunoglobulin function and complement activity, connecting hyperglycemia to systemic hematopoietic inflammatory pathways.[8]

These pathways have implications in medicine; there isn't much data from African populations, where DFIs are very prominent, and the results are generally undesirable. Studying the immunological and metabolic interactions in these contexts may reveal accessible biomarkers for risk classification and inform targeted therapies. The present research sought to check immunoglobulin and complement levels in Sudanese patients with DFIs and to explore their interaction with glycemic indices and ulcer severity. By addressing this gap, we provide novel insights into the immune metabolic drivers of severe DFIs in a resource-limited context.

## METHODS

### *Study design and setting*

This cross-sectional analytical study was fulfilled at Dr. Awaad Medical Center for Diabetic Care, which operates as a private facility in Eastern Sudan. The medical facility provides outpatient services to patients with chronic diseases, including those with diabetes. The research spanned 21 months, from February 2024 to November 2025, and included participants who met the inclusion criteria. The study defined diabetic foot ulcers (DFUs) as complete skin lesions on the feet of patients with diabetes that develop due to peripheral neuropathy, foot ischemia, and subsequent wound infection. The medical team used clinical assessment and microbiological and analytical test results to confirm the diagnosis through bacterial wound identification and blood biomarker measurement. The SINBAD grading system, a vital tool in our research, was used to standardize ulcer severity. This system examines six areas: site (plantar vs. non-plantar), ischemia (lower blood flow), neuropathy (loss of protective sensation), bacterial infection (clinical evidence of infection), ulcer size (area>1 $cm^2$), and tissue depth (superficial vs. deep tissue involvement).

### *Study population*

The research selected fifty-five patients who met SINBAD criteria by being at least eighteen years old and having confirmed diabetic foot infection and documented diabetes mellitus Type 1 or Type 2. The study excluded patients with autoimmune diseases or cancer, or who had received immunosuppressive medication within a short period, because their immunological profiles could be difficult to distinguish. All subjects, in a demonstration of their autonomy, provided their verbal consent, and the institutional review boards granted their ethical approval in accordance with Sudanese research ethics.

### *Data collection*

Structured forms were used to collect demographic and clinical data. The variables consisted of age (in years), sex (male/female), duration of diabetes (in years), and type of diabetes (T1DM or T2DM).

### *Laboratory procedures*

Under sterile settings, blood samples were taken from each participant. A volume of 5 milliliters was extracted and transferred to 3 ml into lithium heparin tubes for biochemical analysis. The remaining blood was added to a tri-potassium ethylene diamine tetra-acetic acid ($K_3$EDTA) tube for HbA1c estimation. The Mindray reagents and the BS-240 Pro chemical analyzer (Serial Number: BC7-2B005644, China) were used to measure FBS, immunoglobulins (IgA, IgG, IgM), and complement proteins (C3, C4).

All tests were done at a qualified diagnostic lab that followed the manufacturer's instructions and its own quality control standards. Reference ranges were established in accordance with regional standards and instrument calibration protocols.

### *Glycemic parameters*

Fasting Blood Sugar (FBS) and glycated hemoglobin (HbA1c) were utilized to evaluate glycemic regulation in all subjects. FBS was quantified in mg/dl and analyzed based on updated clinical thresholds:

*Normal fasting blood sugar*: 70–126 mg/Dl, *Increased fasting blood sugar*: >126 mg/dl

These revised guidelines for pre-prandial glucose targets in diabetic patients, especially those with comorbidities such as diabetic foot ulcers, are of significant importance. HbA1c was represented as a percentage and classified according to recognized diagnostic standards:

*Normal HbA1c*: <6.5%, *Increased HbA1c:* ≥6.5%

This threshold aligns with global standards for diabetes diagnosis.[9]

***Reference range and threshold control***

For analytical reasons, the standard values of immunoglobulins, complement proteins, and glycemic parameters served as threshold controls. Reference ranges were derived from recognized regional laboratory standards and instrument calibration protocols:

*Immunoglobulins:* IgA (0.6–4.0 g/l), IgG (6.0–16.0 g/l), IgM (0.4–2.5 g/l)

*Complement proteins:* C3 (88–180 mg/dl), C4 (15–45 mg/dl)

*Glycemic parameters:* Fasting Blood Sugar (FBS, 70–126 mg/dl), HbA1c (<6.5%)

These thresholds were used to group biomarker readings into low, normal, or high. These categories served as internal controls to assess deviations from standard immunological and glycemic homeostasis in the study population. Reference intervals were based on the manufacturer's reagent insert and laboratory internal quality-control ranges for the Mindray BS-240 Pro platform.

***SINBAD score estimation***

Based on clinical observations throughout the cohort:

*Site:* The majority of ulcers were located on the plantar surface (score=1).

*Ischemia:* Present in a fraction of patients (score=1).

*Neuropathy:* Frequently observed in individuals with chronic diabetes (score=1).

*Bacterial infection:* Verified in every instance (scoring=1).

*Area:* In most cases, the ulcers were bigger than 1 $cm^2$ (scoring=1).

*Depth*: Involvement of subcutaneous tissue or deeper tissues (score=1).

So, the projected SINBAD score for the group is 6, which means that they have severe ulceration and a high risk of complications and delayed recovery.

***Statistical analysis***

The statistical methodology (SPSS version 20, IBN, Chicago) employed in this study was thorough, informed by the distributional characteristics of the data. The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to check for normality, thereby ensuring the robustness of our analysis. Age and IgG were determined to be normally distributed, indicating that parametric tests, such as one-sample and independent samples t-tests, could be used to analyze these variables. Conversely, markers such as IgM, C4, FBS, HbA1c, and, to a lesser extent, C3 exhibited substantial deviation from normality, requiring careful interpretation. Therefore, we used non-parametric alternatives or stratified categorical analysis.

We used descriptive statistics to show the central tendency and variability of all the variables. One-sample t-tests compared biomarker means against the upper reference limit (for markers expected to be elevated) or the lower reference limit (for markers expected to be reduced). We used independent-samples t-tests to examine the levels of immunological markers across male and female patients.

The researcher conducted chi-square tests and crosstabulations to explore how sex variables interact with diabetes types and biomarker levels across strata. The study calculated odds ratios (ORs), mean ± SD, and 95% CI values. The Pearson correlation analysis revealed significant associations among age, diabetes duration, and immunological markers, prompting further modeling. The research used multiple linear regression to study how age and sex variables affect immunoglobulin and complement levels. The study results were statistically significant when p values were less than 0.05.

***Ethical consideration***

The research adhered to the Declaration of Helsinki (2013 revision) and the national research ethics requirements of Sudan. The Institutional Review Board of Port Sudan Ahlia University, Faculty of Medical Laboratory Sciences (REC-PAU 3/4), and the Ethics Committee of Dr. Awaad Medical Center for Diabetic Care provided clearance for the study (AMC, L10). The research participants understood both the research objectives and the experimental procedures, as well as all possible risks associated with the study. The study required illiterate participants to provide consent verbally, with a medical doctor observing the process. The researcher had restricted access to data, and personal identifiers were anonymized to protect patient privacy. Patients retained the right to join or exit the study whenever they wanted while their medical treatment remained unaffected.

## RESULTS

### *Demographic profile of participant*

The study included 55 patients diagnosed with diabetic foot infection at facilities in Eastern Sudan.

**Table 1: Baseline demographic, clinical, glycemic, and immunological characteristics of patients with diabetic foot infections.**

| Variable | N (%), mean±SD (n=55) |
|---|---|
| **Age (years)** | 50.38±15.99 |
| **Sex** | |
| Male | 33 (60) |
| Female | 22 (40) |
| **Type of diabetes** | |
| Type 1 DM | 12 (21.8) |
| Type 2 DM | 43 (78.2) |
| **Duration of diabetes (years)** | 10.34±6.87 |
| **SINBAD score** | |
| Score 6 | 29 (52.7) |
| Score 5 | 2 (3.6) |
| Score 1 | 7 (12.7) |
| **Glycemic state** | |
| Normal FBS<126 mg/dl | 13 (26.3), 117.5±13.0 |
| Elevated FBS>126 mg/dl | 41 (74.5), 217±64.59 |
| Normal HbA1c<6.5% | 7 (12.7), 6.2±0.66 |
| Elevated HbA1c>6.5% | 48 (87.3), 9.5 ± 2.05 |
| **Complement state** | |
| Normal C3 | 43 (78.1), 207.6±5.55 |
| High C3 | 12 (21.8), 188.7±6.14 |
| High C4 | 55 (100), 80.62±11.34 |
| **Immunoglobulin state** | |
| High IGA | 13 (23.6), 4.83±0.63 |
| Normal IGA | 41 (74.5), 2.93±0.96 |
| High IGG | 12 (21.8), 19.9±3.3 |
| Normal IGG | 30 (54.5), 11.57±2.77 |
| Low IGG | 13 (23.6), 4.0±1.48 |
| Low IGM | 29 (52.7), 0.20±0.08 |
| Normal IGM | 25 (45.5), 1.1±0.62 |

The study participants included 60% male patients (n=33) and 40% female patients (n=22). The participants' average age was 50.38±15.99 years, with ages ranging from 17 to 89 years, a median of 50 years, and an interquartile range (IQR) of 39–61 years. The research provided demographic and attribute information, which appears in Table 1.

### *Diabetes type distribution and sex association*

In this study, type 2 diabetes mellitus (T2DM) accounted for 78.2% of the cases, making it the predominant form, with an odds ratio of 3.58 (95% CI: 1.89–6.79). Type 1 Diabetes mellitus (T1DM) accounted for 21.8% of the cases, with an Odds Ratio of 2.00 (95% CI: 0.61–6.58) for males compared to females. The study results showed no link between diabetes type and gender through $\chi^2$ analysis ($\chi^2$=1.439, P=0.230), yet males showed higher T1DM occurrence at 27.3% compared to females at 13.6%.

### *Immunoglobulin and complement levels compared to reference values*

One-sample t-tests were performed to evaluate patient biomarker levels against known laboratory reference values. In comparison to reference values, IgA, C3, and C4 were enhanced (P<0.001), whereas IgM was diminished (P<0.001), and IgG exhibited no significant variation. Comprehensive results are displayed in Table 2.

### *Sex-based comparisons of immune markers*

Independent samples t-tests revealed no statistically significant differences in immunoglobulin or complement levels between male and female patients (p>0.05 across all markers). The average levels of IgA, IgM, C3, and C4 were marginally elevated in men; however, these variations lacked statistical significance (p=0.281, 0.252, 0.161, and 0.214, respectively).

### *Stratified crosstab analysis by sex*

Crosstabulations were conducted to examine sex-based distributions of stratified immunological marker levels. The majority of patients had IgA, IgG, and IgM levels within the normal range, with no significant relationships depending on sex ($\chi^2$= 0.05, p>0.05). However, C3 levels demonstrated a marginal connection, with males exhibiting a higher likelihood of elevated levels ($\chi^2$= 3.482, p=0.062; OR=4.35), a finding that may have intriguing implications. C4 levels were consistently increased among all subjects, preventing statistical comparability.

### *Regression analysis of age and sex as predictors*

We used multiple linear regression models to assess whether age and sex could predict levels of immunological markers. Most models did not show any significance (p> .05); however, C4 did show significance (β=0.290, t= 2.209, p=0.032). The overall model for C4 was also significant (f=3.290, p=0.045), indicating that older patients had higher C4 levels.

### *Correlation analysis*

Pearson correlation analysis revealed a robust positive association between age and diabetes duration (r=0.588, p <0.001), suggesting that older patients exhibited extended disease histories. Furthermore, the duration of diabetes had an inverse correlation with IgA levels (r=–0.273, P= 0.044), suggesting a potential decline in immune function with time. A positive correlation between C3 and C4 (r=

0.597, p<0.001) was noted, indicating synchronized complement activation.

***Duration of diabetes***

Participants had diabetes for a range of 1 to 33 years, with an average of 10.34±6.87 years and a median of 9 years (Table 1). The interquartile range spanned from 5 to 15 years, indicating a wide range of chronicity among the group. This variable had a significant correlation with age (r=0.588, p<0.001), a finding of great importance as it suggests that older patients tend to have longer disease histories. Furthermore, duration exhibited a negative correlation with IgA levels (r = -0.273, p=0.044), indicating a possible immune suppression associated with prolonged disease duration. These findings underscore the importance of disease duration as a key clinical determinant in understanding immunological dysregulation in diabetic foot infections.

***SINBAD score***

The clinical severity of diabetic foot ulcers in this group had a troubling distribution. The SINBAD classification system revealed that more than half of the patients (52.7%) had the highest score of 6, indicating the presence of all six of the most significant ulcer symptoms: plantar location, ischemia, neuropathy, bacterial infection, deep tissue involvement, and an ulcer area greater than 1 $cm^2$. The remaining patients had scores between 1 and 5, with 3.6% achieving a score of 5 and 12.7% achieving a score of 1. This stratification shows a skewed severity profile, with most of the ulcers being advanced and threatening to limbs.

This trend was significantly associated with the duration of diabetes, which ranged from 1 to 33 years, with an average of 10.34 years, and more than half of the population had exceeded 9 years. The Chi-square test examining the correlation between SINBAD score and disease duration produced a statistically significant outcome ($\chi^2$=153.194, df=110, p=0.004), and the Linear-by-Linear Association was highly significant (P<0.001), thereby validating a robust ordinal trend: increased ulcer severity correlated with extended disease duration. Despite the violation of Pearson test assumptions resulting from low anticipated cell counts, the robustness of the linear connection corroborates the clinical finding. In patients with the highest SINBAD score of 6, most had normal IgA levels (36.4%), whereas 16.4% had high IgA levels. Interestingly, none of the patients with a score of 6 had low IgA levels. Conversely, diminished SINBAD scores (1–3) were primarily correlated with normal IgA levels, with very sporadic instances exhibiting elevated or reduced levels. The Pearson Chi-square test revealed a statistically significant correlation between SINBAD score and IgA level ($\chi^2$=19.043, df=10, p=0.040), indicating that ulcer severity may be associated with immunoglobulin regulation, namely IgA expression.

For patients with the highest SINBAD score of 6, most of them had low IgM levels (30.9%), 21.8% had normal levels, and none had high IgM levels. In contrast, lower SINBAD scores (1–4) were more uniformly spread out between the normal and low IgM groups. Only scores 5 and 6 had high IgM values. This pattern indicates a possible correlation between advanced ulceration and diminished IgM expression, aligning with chronic immunological dysregulation in prolonged diabetes. The Pearson Chi-square test ($\chi^2$=33.559, df=10, p<0.001) showed that there was a non-random link between ulcer severity and IgM status.

For individuals with the highest SINBAD score of 6, most (43.6%) had T2DM, and 9.1% had T1DM. There was a reassuringly equitable spread of lower SINBAD scores (1–3) among both categories, with slightly more T1DM patients in scores 1 and 2. This trend suggests that severe ulcers are more prevalent in individuals with T2DM, which aligns with the fact that T2DM can lead to long-term complications affecting blood vessels and nerves. The Pearson Chi-square test yielded a non-significant outcome ($\chi^2$=7.013, df=5, p=0.220), indicating the absence of a robust categorical correlation between diabetes type and SINBAD score. Even if the difference isn't statistically significant, the clinical trend is nevertheless essential. The fact that many T2DM patients have high SINBAD scores indicates that this group requires more intensive foot care and early ulcer screening.

The logistic regression study sought to ascertain independent predictors of severe diabetic foot ulceration (SINBAD score=6), using age, sex, duration of diabetes, diabetes type, and immunoglobulin levels (IgA and IgM) as covariates. The overall model was statistically significant (p<0.001). However, individual predictors did not reach significance because the standard errors were too high and the predictions were too perfect. This was probably because 52.7% of the cases were very severe. These results suggest that while duration and immunological markers may influence ulcer severity, a more extensive and balanced dataset is needed to validate their independent prognostic significance.

***Glycemic status***

The glycemic pattern of patients with diabetic foot ulcers in our sample was significantly irregular. With a modified threshold of FBS >126 mg/dl, 74.5% of patients (n=41) were categorized as having increased fasting blood sugar levels. Notably, 87.3% (n=48) exhibited HbA1c levels of greater than 6.5%, indicating that almost all patients experienced chronic glycemic dysregulation. These findings highlight the metabolic load experienced by this population and emphasize the urgent need for comprehensive glycemic and wound care strategies. The average FBS was 191.0±71.9 mg/dl (median 167, IQR: 133–232), whereas the average HbA1c was 9.12±2.25% (median 8.7, IQR: 7.4–10.6). Crosstab analysis indicated a significant association between low IgM and elevated

HbA1c ($\chi^2$=7.017, p=0.030). Conversely, C3 exhibited a negligible correlation with HbA1c levels (p=0.096), whereas C4 was consistently raised across nearly all individuals. Severe ulceration (SINBAD score 6) was more common in patients with elevated HbA1c and high FBS, although chi-square tests could not achieve statistical significance. FBS levels were convincingly and substantially correlated with C3 status ($\chi^2$=6.033, p= 0.049), indicating a relationship between complement activation and short-term glycemic dysregulation. A multivariable logistic regression model was developed to investigate the factors contributing to increased fasting blood sugar levels. Univariate screening indicated potential involvement for complement C3 and IgM, which were included in the final model. Low IgM levels were identified as a statistically significant predictor (OR= 0.842, 95% CI: 0.712–0.996, p=0.045), suggesting a potential association between immune suppression and hyperglycemia. These findings could have important clinical implications. C3 exhibited positive trends toward connection (P=0.096); nevertheless, their broad confidence intervals and marginal significance underscore the constraints imposed by sample size and the elevated prevalence of dysglycemia. A parallel linear regression model using continuous FBS values corroborated the same directional effect, revealing a negative correlation for IgM (β= -0.31, p=0.038) and C3, which approached significance (β=0.22, p=0.067). Conversely, the determinants of increased HbA1c were more distinctly delineated. Both age and diabetes duration exhibited robust and persistent correlations with chronic hyperglycemia. The logistic regression model indicated that age correlated with heightened odds of raised HbA1c (OR=1.072, 95% CI: 1.015–1.132, p=0.012), whereas the duration of diabetes had a more pronounced effect (OR= 1.118, 95% CI: 1.026–1.219, p=0.009). These findings align with biological assumptions, as prolonged exposure to metabolic dysregulation and vascular impairment results in persistent hyperglycemia. Despite the majority of patients exhibiting increased HbA1c levels, which could potentially affect model stability, the correlations persisted robustly. Linear regression validated these patterns, indicating that age and duration exhibited positive correlations with HbA1c (β=0.29, p=0.008 and β=0.33, p=0.004, respectively), underscoring their significance as primary factors in diabetic worsening within this cohort.

**Table 2: Comparison of immunological and glycaemic biomarkers with reference ranges in patients with diabetic foot infections.**

| Biomarker | Mean±SD | Reference range | P value | Status |
|---|---|---|---|---|
| **IGA (g/l)** | 3.38±1.20 | 0.6-4.0 | <0.001 | Elevated |
| **IGG (g/l)** | 11.60±6.00 | 6.0-16.0 | 0.464 | Normal |
| **IGM (g/l)** | 0.66±0.70 | 0.4-2.5 | <0.001 | Reduced |
| **C3 (mg/dl)** | 192.80±9.89 | 88-180 | <0.001 | Elevated |
| **C4 (mg/dl)** | 80.62±11.34 | 15-45 | <0.001 | Markedly elevated |
| **FBS (mg/dl)** | 191±71.95 | 70-126 | <0.001 | Markedly elevated |
| **HbA1c (%)** | 9.12±2.25 | 4.0-6.5 | <0.001 | Markedly elevated |

## DISCUSSION

This study provides detailed information on dysregulation of immunoglobulins and complements in Sudanese patients with DFIs, emphasizing their correlation with glycemic management and ulcer severity. The results demonstrated a unique immune profile, characterized by elevated levels of IgA, C3, and C4, accompanied by decreased IgM, and were significantly correlated with diabetic indices (HbA1c and FBS).

The demographic analysis indicated that a majority of male patients (60%) had an average age of 50.38 years. This corresponds with global epidemiological patterns, suggesting that diabetic foot problems are more commonly observed in middle-aged males due to procrastination in seeking care and elevated incidences of peripheral vascular disease.[10] These findings have significant implications for patient care. T2DM constituted 78.2% of cases, stratified with regional and global statistics that identify T2DM as the fundamental cause of diabetic foot complications.[6] The male-to-female ratio for T1DM patients was significantly higher, at 27.3% compared with 13.6%. However, the correlation between diabetes type and sex was not statistically significant. While it could be attributed to variability in sample populations or to genetic variation among individuals, the observed odds ratio for T2DM of 3.58, indicating the prevalence of the spot pattern among T2DM cases was 3.58 times that of controls, does suggest a trend which requires further investigation in larger groups.

In this cohort, significantly raised levels of serum IgA suggest that there is an active immune response at the body's mucous membranes and elsewhere in the body. This is a crucial finding in diabetes research. IgA levels have been shown to increase in chronic inflammatory and infectious conditions, indicating persistent antigenic stimulation at the ulcer site.[10] Conversely, a diminished IgM level signifies a compromised first line of immune defense. Reduced IgM levels have been observed in individuals with diabetes who experience recurrent infections, potentially attributable to glycation-induced structural alterations that impair antibody efficacy.[11] The identified inverse association between diabetes duration and IgA levels may indicate progressive immunological

exhaustion in prolonged diabetes, aligning with research describing immune senescence in chronic hyperglycemia.[4]

The elevation of C3 and C4 above laboratory reference limits suggests persistent complement activation, particularly the age-related increase in C4 levels, which underscores the importance of our findings. These findings suggest continuous complement activation, a key factor in the chronic, low-grade inflammation associated with diabetic complications.[7] C4 levels were significantly higher in all members of this group. This conclusion, while somewhat unexpected, can be explained by various possible reasons. C4 serves as an acute-phase reactant and may increase in response to ongoing inflammatory stimuli associated with chronic infection and tissue damage.[7] Secondly, persistent diabetes, inflammation, and immunological dysregulation have been demonstrated to affect complement activation pathways.[3,4] Ultimately, the localized inflammatory load in advanced diabetic foot infections may lead to persistent complement overexpression at the population level.[6] Consequently, the consistently heightened C4 levels indicate inflammatory complement activation rather than an analytical artifact.

In fact, a raised complement activity that correlates with damage to the endothelial layer and impaired wound healing is especially relevant to the high scores observed in this group on the SINBAD ulcer.[12] This research could have implications for developing new treatments to address the activation of the complement system in diabetes-related conditions, providing the possibility of better patient outcomes.

Significantly, IgG levels remained within normal ranges, in contrast to findings of higher IgG subclasses in individuals with refractory infections.[10] This may indicate variations in microbial load or immunological fatigue within the examined population.

Our comparative analyses of immunological markers based on sex did not reveal statistically significant differences. However, we found that males had slightly elevated levels of IgA, IgM, C3, and C4. The crosstab inspection indicated a minor correlation between male sex and increased C3 levels ($\chi^2$=3.482, p=0.062; OR=4.35). This finding proposes a potential sex-related modulation of complement activity, with significant implications for our understanding of immunological responses in different sexes. Importantly, these findings align with the work of Kheiralla et al, who documented increased C3 levels in individuals with diabetic foot, especially in those with active infections.[6] Significantly, elevated SINBAD scores correlated with diminished IgM and modified IgA levels, indicating that humoral immune dysregulation contributes to worse wound outcomes. Prior studies suggest that diminished IgM impairs opsonization and bacterial eradication, increasing susceptibility to severe infections and protracting ulcer healing.[13] This is consistent with the high percentage of individuals exhibiting advanced (scoring 6) ulcers in our cohort.

In this study, the majority of patients exhibited extensive ulceration, with 52.7% assigned a SINBAD score of 6. Elevated HbA1c and elevated FBS were both correlated with higher advanced SINBAD scores; however, these associations did not achieve statistical significance. The clinical trend is significant: patients with chronic hyperglycemia exhibited more severe ulceration, indicating the recognized impact of inadequate glycemic management on impaired wound healing.[8]

Remarkably, ulcer severity was associated with modified immunoglobulin profiles. Patients with severe ulcers often displayed diminished IgM levels and inconsistent IgA expression, suggesting that humoral immune dysregulation plays a role in the advancement of DFIs. These findings boost the observations that prolonged hyperglycemia results in immunological fatigue and diminished bacterial clearance, thereby exposing individuals to refractory ulceration, such as ulcers that do not respond to standard treatments or that lead to critical entanglements.[4]

Regression analysis revealed that age was a significant predictor of C4 levels (p=0.032), with the overall model attaining statistical significance (p=0.045). This suggests that complement activation may increase with age, potentially leading to prolonged wound healing and heightened susceptibility to infection. Understanding these age-related immunological alterations could provide valuable insights into chronic inflammatory conditions, which may indicate the accumulation of metabolic and vascular stress.[4]

Almost all patients (87.3%) exhibited increased HbA1c levels, indicating a persistent metabolic dysregulation. Hyperglycemia is a recognized contributor to the diminished function of neutrophils and lymphocytes, increasing vulnerability to infections.[8] Our regression analysis revealed that low IgM is a predictor of hyperglycemia (p=0.030), indicating a bidirectional relationship: inadequate glycemic control may hinder antibody formation, whereas diminished immune defenses may facilitate recurrent infections and exacerbate metabolic instability. These findings present exciting opportunities for further research in this area. Our research identified dysregulation of complement as another significant characteristic. We found a robust correlation between C3 levels and FBS state (p=0.049). Patients with elevated FBS levels were more likely to have normal C3 levels rather than elevated ones. This suggests that short-term glycemic variations may influence complement activation differently than prolonged HbA1c elevation, reinforcing the robustness of our findings. The amalgamation of immunological markers (notably IgM and complement proteins) with glycemic indices (FBS and HbA1c) provides novel insights into the pathophysiology of DFI. The notable connections between IgM–HbA1c and C3–FBS indicate a close interrelation between immunological dysfunction and metabolic regulation. In resource-limited frameworks like Sudan, assessing

fundamental immunological markers (IgM, C3, C4) in synchronization with glycemic indices may avail as an economical predictive tool for identifying individuals susceptible to severe ulcers and prolonged healing. By acting promptly on any indications of a failure of the immune system, it may be possible to launch more assertive treatments sooner, for instance, through more stringent glucose monitoring, quicker treatment of wounds, and possibly other immunomodulatory therapies. The main drawbacks of the study are its relatively small sample size and cross-sectional design. This restricts the drawing of firm conclusions about cause and effect. The high prevalence of severe DSIs may have diminished heterogeneity in ulcer severity, hence constraining statistical power. Given the small sample size and the high prevalence of severe ulceration in the cohort, multivariable regression models may be prone to overfitting and reduced generalizability. More extensive prospective investigations are necessary to confirm the independent prognostic significance of immunoglobulin and complement indicators. Future long-term studies should investigate whether improving glycemic control leads to normalization of IgM and complement activity and whether immune-targeted treatments improve wound-healing outcomes.

## CONCLUSION

Sudanese diabetic patients with foot infections exhibited significantly elevated complement levels and reduced IgM levels, both of which are associated with diabetic foot. Those with diabetes have their immune response impaired by prolonged episodes of high blood glucose. This increases the risk of infection and increases the severity of any ulcers that may appear on the foot. Those in this high-risk category may benefit from being assessed using various immunological and metabolic markers to improve predicted outcomes and risk classification.

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## REFERENCES

1. Armstrong DG, Tan TW, Boulton AJM, Bus SA. Diabetic Foot Ulcers: A Review. JAMA. 2023;330(1):62-75.
2. Swaminathan N, Awuah WA, Bharadwaj HR, Roy S, Ferreira T, Adebusoye FT, et al. Early intervention and care for Diabetic Foot Ulcers in Low and Middle Income Countries: Addressing challenges and exploring future strategies: A narrative review. Health Sci Rep. 2024;7(5):e2075.
3. Dawi J, Tumanyan K, Tomas K, Misakyan Y, Gargaloyan A, Gonzalez E, et al. Diabetic Foot Ulcers: Pathophysiology, Immune Dysregulation, and Emerging Therapeutic Strategies. Biomedicines. 2025;13(5):1076.
4. Berbudi A, Rahmadika N, Tjahjadi AI, Ruslami R. Type 2 Diabetes and its Impact on the Immune System. Curr Diabetes Rev. 2020;16(5):442-9.
5. Fejfarová V, Jirkovská A, Dubský M, Game F, Vydláková J, Sekerková A, et al. An Alteration of Lymphocytes Subpopulations and Immunoglobulins Levels in Patients with Diabetic Foot Ulcers Infected Particularly by Resistant Pathogens. J Diabetes Res. 2016;2016:2356870.
6. Kheiralla ZM, Maklad SS, Ashour SM, El-Sayed Moustafa E. Association of complement C3 and interleukin-1 with foot infections in diabetic patients. Eur J Microbiol Immunol (Bp). 2012;2(3):220-30.
7. Ajjan RA, Schroeder V. Role of complement in diabetes. Mol Immunol. 2019;114:270-7.
8. Holt RIG, Cockram CS, Ma RCW, Luk AOY. Diabetes and infection: review of the epidemiology, mechanisms and principles of treatment. Diabetologia. 2024;67(7):1168-80.
9. American Diabetes Association Professional Practice Committee. Summary of Revisions: Standards of Care in Diabetes-2025. Diabetes Care. 2025;48(1):S6-13.
10. Fejfarová V, Jirkovská A, Dubský M, Game F, Vydláková J, Sekerková A, et al. An Alteration of Lymphocytes Subpopulations and Immunoglobulins Levels in Patients with Diabetic Foot Ulcers Infected Particularly by Resistant Pathogens. J Diabetes Res. 2016;2016:2356870.
11. Costantini E, Carlin M, Porta M, Brizzi MF. Type 2 diabetes mellitus and sepsis: state of the art, certainties and missing evidence. Acta Diabetol. 2021;58(9):1139-51.
12. Hui W, Yaping Y, Liqing G, Zhigang M, Peng Yinbo, Jing W. Study on the correlation between SINBAD system score and wound pH value in diabetic foot sarcopenia. J Tissue Viability. 2025;34(3):100915.
13. Dasari N, Jiang A, Skochdopole A, Chung J, Reece EM, Vorstenbosch J, et al. Updates in Diabetic Wound Healing, Inflammation, and Scarring. Semin Plast Surg. 2021;35(3):153-8.

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