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Immune-inflammatory Markers in Diabetic Peripheral Neuropathy and their Association with Quality of Life

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ABSTRACT

Diabetic peripheral neuropathy (DPN) is a disabling complication of type 2 diabetes, associated with neuropathic pain and reduced quality of life (QoL). Inflammation is implicated in DPN pathogenesis. We investigated associations between inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), and QoL in DPN patients in Eastern Iran.

One hundred seventeen type 2 diabetic patients from two from two Zabol hospitals/clinics were enrolled. QoL was assessed using WHOQOL-BREF questionnaire, and neuropathy was evaluated using Michigan neuropathy screening instrument (MNSI). Serum CRP and IL-6 levels were measured. Analyses included t-tests, analysis of variance, and linear regression in SPSS.

The prevalence of DPN among patients was 56.4%. Patients with DPN exhibited higher levels of CRP (mean: 4.2±1.8 mg/L) and IL-6 (mean: 5.6±2.1 pg/mL) compared with the non-neuropathic group. Additionally, QoL, particularly in the physical domain, was significantly lower in patients with higher levels of these inflammatory markers. However, multiple linear regression analysis after adjusting for confounding variables (including age, sex, BMI, diabetes duration, and HbA1c) revealed that neither CRP, IL-6, nor BMI were independently associated with QoL in the final model.

The overall regression model was not statistically significant, indicating that the measured variables collectively explained only a small fraction of QoL variance. In univariate analysis, elevated CRP and IL-6 correlated with poorer QoL in neuropathic patients, but these associations did not remain significant after adjusting for confounders. Our findings highlight the need for further research incorporating unmeasured factors, such as pain severity, depression, and medication use, to better understand determinants of QoL in this population.

Keywords: C-reactive protein; Diabetic Neuropathies; Immunology; Inflammation; Interleukin-6; Quality of life; Diabetes mellitus, Type 2

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INTRODUCTION

Type 2 diabetes mellitus is a common metabolic disorder with an increasing prevalence worldwide, particularly in developing countries, including Iran.[1] The disease is accompanied by numerous microvascular and macrovascular complications, among which diabetic peripheral neuropathy (DPN) is considered one of the most disabling and prevalent.[2] The burden of diabetic complications is particularly high in developing countries, such as Iran, where access to comprehensive diabetes care may be limited and socioeconomic factors exacerbate health outcomes. Understanding region-specific risk profiles, including inflammatory markers, is therefore crucial for developing targeted interventions in resource-constrained settings. DPN, characterized by progressive damage to peripheral nerves, often manifests as sensory and painful symptoms, such as burning pain, paresthesia, allodynia, and loss of protective sensation in the feet.[3] This complication not only significantly increases the risk of foot ulcers, infection, and amputation but also profoundly affects patients' quality of life (QoL), leading to impairments in daily functioning, sleep, mood, and social relationships.[4,5]

Although chronic hyperglycemia is the primary driver of DPN, evidence increasingly implicates systemic inflammation and immune activation in its pathogenesis and progression.[6,7,16] Key inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6)—indicators of low-grade inflammation—are elevated in diabetes and correlate with neuropathy severity and neural dysfunction.[8,9] Proposed mechanisms include oxidative stress, damage to the vasa nervorum, and disrupted neural signaling.[10]

Despite this pathophysiological link, few studies have concurrently examined how these inflammatory markers affect the multidimensional QoL in DPN patients. QoL encompasses physical, psychological, social, and environmental well-being, each notably impaired by neuropathic symptoms.[11] Research in varied populations, particularly in regions with distinct socioeconomic profiles, such as eastern Iran, could yield clinically relevant insights for tailored interventions. Previous Iranian studies have predominantly addressed DPN epidemiology and conventional risk factors.[12,13] For instance, longer diabetes duration and poor glycemic control were associated with higher DPN prevalence,[14] and neuropathy was linked to poorer physical and psychological QoL.[15] However, the potential mediating role of systemic inflammation between DPN and QoL remains unexplored in this setting.

Accordingly, this study aimed to investigate the association between systemic inflammatory markers (CRP and IL-6) and both the presence of neuropathy and multidimensional QoL in patients with type 2 diabetes in Zabol County, eastern Iran. Specifically, we sought to determine the prevalence of DPN and characterize inflammatory profiles in this population, compare CRP and IL-6 levels between patients with and without DPN, and evaluate the relationship of these markers with various QoL domains. Furthermore, we aimed to assess the independent predictive value of inflammatory markers for QoL after accounting for key confounders. We hypothesized that elevated levels of CRP and IL-6 would be associated with a higher likelihood of DPN and poorer QoL scores, even after adjustment for traditional risk factors, such as glycemic control and diabetes duration. The findings may enhance our understanding of the pathophysiological interplay between inflammation and patient-centered outcomes in DPN. Ultimately, this could inform more integrated management strategies that combine anti-inflammatory approaches with conventional glycemic control.

MATERIALS AND METHODS

Study Design

This cross-sectional analytical study was conducted between 2024 and 2025 at healthcare centers in Zabol County, including 2 hospitals, the Diabetes Clinic, and the Neurology Clinic.

Inclusion and Exclusion Criteria

Inclusion criteria for patients with type 2 diabetes were: age ≥ 18 years, diagnosis of type 2 diabetes with a minimum duration of 5 years, residence in Zabol, and provision of informed consent. Patients were excluded if they had a history of non-diabetic neuropathy, such as alcoholic, vitamin B_{12} deficiency, or uremic neuropathy; active neoplastic or autoimmune diseases; use of neurotoxic drugs or corticosteroids within the past month; history of gastrointestinal surgery; or pregnancy.

Sample Size Calculation

The sample size was calculated using the single

proportion formula, assuming a DPN prevalence of approximately 50%, a type I error of 0.05, and a precision of 0.1, resulting in 117 participants. Convenience sampling was employed.

Data Collection Tools

Demographic and Clinical Questionnaire

Information regarding age, sex, marital status, education, occupation, economic status, duration of diabetes, type of treatment, and level of physical activity was collected.

Michigan Neuropathy Screening Instrument (MNSI)

This instrument consisted of 2 parts:

Part A: Fifteen self-reported questions regarding neuropathic symptoms, such as numbness, burning pain, and cramping. A score ≥ 7 was considered indicative of neuropathy.

Part B: Clinical examination of the feet, including assessment of skin changes, vibration sensation using a 128-Hz tuning fork, Achilles reflex, and light touch sensation using a 10-g monofilament. A score ≥ 2.5 was considered positive.

A final diagnosis of DPN was made if both Part A and Part B were positive.

World Health Organization Quality of Life-BREF (WHOQOL-BREF) Questionnaire

This 26-item questionnaire assessed QoL across 4 domains: physical health (7 items), psychological health (6 items), social relationships (3 items), and environmental health (8 items). Responses were rated on a 5-point Likert scale (1 = very poor to 5 = very good). Final scores were transformed to a 0–100 scale.

Measurement of Laboratory Indicators

HbA1c: The most recent test result from the previous 3 months was extracted from the medical records.

Inflammatory Markers: Five mL of fasting venous blood were collected from each patient. Serum CRP level was measured using the latex-enhanced immunoturbidimetry method. Serum IL-6 level was quantified using a commercial sandwich enzyme-linked immunosorbent assay kit (Karmania Pars Gene Co., Iran) according to the manufacturer's instructions. This assay employs specific monoclonal antibodies against human IL-6 and is validated for the quantitative measurement of IL-6 in human serum.

Statistical Analysis

Data were analyzed using SPSS software version 26. Continuous variables were reported as mean±SD. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. For comparing means between 2 independent groups, the independent t-test was used for normally distributed data, and the Mann–Whitney U test was used for non-normally distributed data. For comparisons among more than 2 groups, one-way analysis of variance (ANOVA) was employed for normally distributed data, and the Kruskal–Wallis test was used for non-normally distributed data. Associations between continuous variables were evaluated using Pearson correlation coefficient for normally distributed data and Spearman rank correlation for non-normally distributed data. Multiple linear regression was performed to identify independent predictors of QoL. Variables with $p<0.2$ in univariate analysis or those with established clinical importance, including age, sex, diabetes duration, and BMI, were entered into the multiple linear regression model using the Enter method. A significance level of $p<0.05$ was considered for all tests.

RESULTS

Demographic and Clinical Characteristics

In this study, 117 patients with type 2 diabetes with a mean age of 62.22±8.4 years (range: 41–86 years) were examined. Fifty-nine percent were male and 41% were female. The mean duration of diabetes was 11.69±2.43 years, and the mean body mass index (BMI) was 26.52±2.22 kg/m^2. Regarding economic status, the highest frequency was related to poor and very poor levels (a total of 71.8%), a profile indicative of the socioeconomic challenges often faced by patient populations in resource-limited settings. Other demographic and clinical characteristics of the patients are presented in Table 1.

Table 1. Demographic and clinical characteristics of the study participants (N=117)

Characteristic	Category or unit	Value
Age	Mean±SD, y	62.22±8.4
Gender	Male, n (%)	69 (59.0)
	Female, n (%)	48 (41.0)
Diabetes duration	Mean±SD, y	11.69±2.43
Body mass index	Mean±SD, kg/m^2	26.52±2.22
Economic status	Very poor, n (%)	29 (24.8)
	Poor, n (%)	55 (47.0)
	Moderate, n (%)	31 (26.5)
	Good, n (%)	2 (1.7)
DPN prevalence	With DPN, n (%)	66 (56.4)
	Without DPN, n (%)	51 (43.6)

DPN: diabetic peripheral neuropathy; SD: standard deviation.

Prevalence and Characteristics of Diabetic Peripheral Neuropathy

According to the MNSI criteria, 66 patients (56.4%) were diagnosed with DPN. The mean duration of neuropathy in this group was 2.91±2.85 years. The most common neuropathic symptoms in patients with DPN included burning pain (68.2%), hypersensitivity to touch (65.2%), and pain upon contact with bedsheets (65.2%). The frequency of other neuropathic symptoms in both the affected and non-affected groups is shown in Table 2.

Comparison of Metabolic and Inflammatory Indicators Between Patients with and Without DPN

The mean HbA1c in the total sample was 7.30±0.24%. Patients with DPN had a higher HbA1c level compared with the non-neuropathic group (7.36±0.23% vs 7.24±0.26%; p=0.008). In addition, the levels of inflammatory indicators were significantly increased in the DPN group; the mean CRP in patients with DPN was 4.2±1.8 mg/L compared with 3.0±1.2 mg/L in the non-affected group (p<0.001). Similarly, the IL-6 level in the DPN group was significantly higher (5.6±2.1 vs 4.2±1.8 pg/mL; p=0.002). The details of this comparison are provided in Table 3.

Quality of Life in Patients with and Without DPN

The total QoL score was significantly lower in patients with DPN compared with patients without neuropathy (52.58±15.8 vs. 60.39±6.05; p<0.001). Examination of different QoL domains showed that patients with DPN had lower scores in the physical health domain (58.17±7.25 vs 76.03±5.70; p<0.001) and social relationships domain (47.60±15.52 vs 59.16±12.61; p<0.001). However, no significant difference was observed between the two groups in terms of psychological and environmental health domains. The complete results of this comparison are summarized in Table 3.

Association of Inflammatory Markers with Quality of Life

Pearson correlation analysis showed that higher levels of CRP and IL-6 had a significant inverse correlation with the total QoL score (r=−0.31, p=0.001 and r=−0.27, p=0.003, respectively). This inverse correlation was particularly prominent in the physical health domain, where CRP and IL-6 were correlated with the physical health score with correlation coefficients of −0.34 and −0.29, respectively (p<0.01). A significant correlation was also observed between inflammatory markers and the social relationships domain, while their association with psychological and environmental health did not reach statistical significance (Table 4).

Factors Associated with Quality of Life

Analysis of variance results showed that the level of physical activity had a significant positive association with the QoL score (F = 14.97, p<0.001). Patients who

had moderate or high physical activity reported higher QoL scores compared with those with low or very low physical activity. In addition, better economic status was associated with higher quality of life (p=0.037). In contrast, no significant association was observed between BMI and quality of life (p=0.075).

Association of Glycemic Control with Neuropathic Symptoms

In supplementary analyses, higher HbA1c levels showed a significant association with the occurrence of specific neuropathic symptoms, including temperature sensation impairment (p=0.004), muscle cramps (p=0.047), symptom exacerbation at night (p=0.029), and foot numbness while walking (p=0.008).

Multiple Linear Regression Analysis for Predicting Quality of Life

To investigate the independent role of inflammatory markers and other clinical variables in predicting quality of life, a multiple linear regression model using the Enter method was performed. The dependent variable was the total quality of life score, and the independent variables included age, sex, BMI, diabetes duration, HbA1c, CRP, and IL-6. The results of this analysis are presented in Table 5.

Table 2. Frequency of neuropathic symptoms in patients with and without DPN

Neuropathic symptom	With DPN (n=66), n (%)	Without DPN (n=51), n (%)
Burning pain	45 (68.2)	10 (19.6)
Hypersensitivity to touch	43 (65.2)	8 (15.7)
Pain from bedsheet contact	43 (65.2)	7 (13.7)
Numbness	38 (57.6)	12 (23.5)
Muscle cramps	32 (48.5)	9 (17.6)
Tingling sensation	30 (45.5)	6 (11.8)

[a]DPN: diabetic peripheral neuropathy.

Table 3. Comparison of metabolic, inflammatory, and quality of life indicators between patients with and without DPN

Variable	With DPN (n=66)	Without DPN (n=51)	*p*
HbA1c, %	7.36±0.23	7.24±0.26	.008
CRP, mg/L	4.2±1.8	3.0±1.2	<.001
IL-6, pg/mL	5.6±2.1	4.2±1.8	.002
Total QoL score	52.58±15.8	60.39±6.05	<.001
Physical health domain	58.17±7.25	76.03±5.70	<.001
Social relationships domain	47.60±15.52	59.16±12.61	<.001
Psychological health domain	51.07±10.34	51.35±8.24	.962
Environmental health domain	60.46±9.11	62.25±9.54	.304

CRP: C-reactive protein; DPN: diabetic peripheral neuropathy; IL-6: interleukin-6; QoL: quality of life.

Table 4. Correlation coefficients (*r*) between inflammatory markers and quality of life domains

QoL domain	Correlation with CRP (*r*)	*p*	Correlation with IL-6 (*r*)	*p*
Total QoL score	−0.31	.001	−0.27	.003
Physical health	−0.34	<.001	−0.29	.002
Psychological health	−0.18	.052	−0.16	.085
Social relationships	−0.22	.019	−0.19	.037

Environmental health	−0.15		.106	−0.12	.191

CRP: C-reactive protein; IL-6: interleukin-6; QoL: quality of life.

Table 5. Multiple linear regression analysis for predictors of total quality of life score

Predictor	B	SE	β	*t*	*p*	95% CI for B
Constant	70.23	27.13	—	2.59	0.011	16.67 to 123.79
CRP, mg/L	−0.79	0.62	−.118	−1.28	0.204	−2.02 to 0.44
IL-6, pg/mL	−0.52	0.52	−.093	−1.01	0.317	−1.55 to 0.51
BMI, kg/m^2	−1.20	0.52	−.324	−2.29	0.024	−2.24 to −0.16
Diabetes duration, y	−0.26	0.31	−.077	−0.85	0.395	−0.88 to 0.35
Gender (male vs female)	−0.15	1.52	−.009	−0.10	0.922	−3.16 to 2.86
Age, y	0.06	0.09	.059	0.65	0.517	−0.12 to 0.24
HbA1c, %	3.15	4.76	.094	0.66	0.510	−6.31 to 12.61

Model summary: R^2=0.108; adjusted R^2=0.051; F (7,109)=1.888; p=0.078.

BMI: body mass index; CI: confidence interval; CRP: C-reactive protein; HbA1c: hemoglobin A1c; IL-6: interleukin-6; SE: standard error.

Multiple linear regression analysis was performed to identify independent predictors of QoL. The overall model was not statistically significant (F (7,109) = 1.888, p=0.078, R^2=0.108), indicating that the included variables, including age, sex, BMI, diabetes duration, HbA1c, CRP, and IL-6, collectively explained only 10.8% of the variance in QoL scores. Because the overall regression model was not statistically significant (p=0.078), the individual p values should be interpreted with caution. Although BMI showed a p value of .024 in the table, this cannot be interpreted as evidence of an independent association given the nonsignificant overall model. None of the predictors, such as CRP (p=0.204), IL-6 (p=0.317), and BMI (p=0.024), demonstrated a statistically reliable independent association with QoL.

DISCUSSION

This cross-sectional study investigated the association between systemic inflammatory markers, such as CRP and IL-6, and quality of life in patients with type 2 diabetes in eastern Iran, with a specific focus on those with DPN. The key findings were as follows: 1) a high prevalence of DPN (56.4%); 2) significantly elevated levels of CRP and IL-6 in patients with DPN compared to those without; 3) a significant negative correlation between inflammatory markers and QoL scores in univariate analyses; and 4) the lack of a significant independent association for any variable, including BMI, in the multivariate regression model, which itself was not statistically significant (p=0.078). The nonsignificant overall regression model suggests that the relationship between inflammation, metabolic factors, and QoL is more complex than can be captured by our measured variables. Other unmeasured factors, which are discussed in the limitations, likely play important roles. These results offer a nuanced understanding of the complex interplay between inflammation, metabolic factors, and patient-reported outcomes in diabetic neuropathy. The high prevalence of DPN in our study may reflect challenges in glycemic management and access to regular screening in a resource-limited setting, such as eastern Iran, where a majority of participants reported poor economic status. The observed prevalence of DPN (56.4%) aligns with findings from other regional studies in Iran, which report rates between 50% and 60% in populations with long-standing diabetes.[14] This high prevalence underscores DPN as a major public health concern in the region, likely influenced by factors such as glycemic variability, longer disease duration, and potentially suboptimal management strategies in resource-limited settings.[13,14]

Our study corroborates a growing body of evidence implicating low-grade systemic inflammation in the pathophysiology of DPN.[6,7,16] The significantly higher levels of CRP and IL-6 in the DPN group are consistent with previous research demonstrating that proinflammatory cytokines contribute to endothelial dysfunction, oxidative stress, and direct neural damage.[10,17] For instance, Herder et al[6] showed that elevated levels of IL-6 and CRP predicted the incidence and progression of distal sensorimotor polyneuropathy in a large cohort study. The inflammatory milieu is believed to disrupt the vasa nervorum and impair

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neuronal repair mechanisms, thereby accelerating neuropathy progression.[10]

A significant novel contribution of this study is the detailed examination of QoL across multiple domains. As expected, patients with DPN reported substantially lower scores in total QoL, physical health, and social relationships. The physical burden of neuropathic pain and sensory loss directly impairs mobility and daily activities, explaining the profound impact on the physical health domain, while the impairment in social relationships may stem from activity limitations, social withdrawal due to chronic pain, and the psychological toll of a disabling chronic condition.[4,5] Interestingly, no significant differences were found in psychological or environmental health domains. This may suggest that in this specific population, the immediate physical and social consequences of DPN are more salient than generalized psychological distress or perceptions of the environment, or it may reflect the insensitivity of the environmental domain to disease-specific changes.

The univariate correlations confirmed that higher inflammatory activity is associated with poorer QoL, particularly in the physical domain. This aligns with the concept that inflammation may not only drive nerve damage but also amplify pain perception and contribute to sickness behavior, thereby directly reducing well-being.[18]

The multivariate regression analysis yielded a nonsignificant overall model (p=0.078), indicating that our measured variables collectively explained only a small fraction (10.8%) of the variance in QoL scores. Given the nonsignificant model, no individual predictor, including BMI, CRP, or IL-6, can be reliably interpreted as having an independent association with QoL. The apparent correlation between inflammatory markers and QoL observed in univariate analyses did not persist after adjustment for confounders, and the borderline association of BMI (p=0.024 in the model, but p=0.075 in univariate analysis) was not statistically robust. Several interpretations are plausible. First, the relatively modest sample size (N=117) may have limited statistical power to detect modest effect sizes. Second, unmeasured confounders, such as depression, neuropathic pain severity, and medication use, which are discussed in the limitations, likely play important roles in determining QoL. Third, the relationship between inflammation, obesity, and QoL is complex and may involve bidirectional pathways that cross-sectional designs cannot disentangle. Rather than concluding that BMI is an independent predictor, our findings suggest that the determinants of QoL in DPN patients are multifactorial and not fully captured by the variables included in this study.

Our results, showing a nonsignificant overall regression model, contrast with some prior studies that reported independent associations between inflammation and QoL or neuropathy severity.[6,9] However, those studies had larger sample sizes or included different sets of adjustment variables. Our findings do not refute a role for inflammation in DPN—given the significantly elevated CRP and IL-6 levels in the DPN group—but rather suggest that the effect of inflammation on QoL may be indirect or mediated through other pathways not captured in our model.

The lack of significant associations for HbA1c in the regression model was also noteworthy. While hyperglycemia is the primary etiological driver of DPN,[2] its effect on cross-sectional QoL measures may be indirect or may require larger sample sizes to detect. Our findings highlight that in this population, the measured metabolic and inflammatory variables explained limited variance in QoL, suggesting that other factors, such as pain severity, psychological distress, and socioeconomic barriers, may be more direct determinants of patient well-being.

This study has several strengths. It employed standardized and validated tools for both the diagnosis of DPN (MNSI) and the assessment of QoL using the WHOQOL-BREF questionnaire. Specific inflammatory biomarkers (CRP and IL-6) were measured directly from serum, and the analysis adjusted for a comprehensive set of key confounding variables. Furthermore, the focus on a population from eastern Iran with distinct socioeconomic characteristics provides valuable context-specific data that can inform regional healthcare strategies.

However, the findings must be interpreted in light of certain limitations. The cross-sectional design precludes the establishment of causal relationships between inflammatory markers, neuropathy, and quality of life. The use of convenience sampling from tertiary healthcare centers in a single geographical region (Zabol) may limit the generalizability of the results to other populations or community settings. Although validated, the diagnosis of DPN was based on a clinical screening tool (MNSI) and not confirmed by more definitive electrophysiological testing. Finally, other potential confounding factors, such as detailed dietary

habits, specific medication use, such as statins and nonsteroidal anti-inflammatory drugs (NSAIDs), or coexisting psychiatric conditions like depression, were not assessed and could influence the observed associations.

Overall, this study confirms the high burden of DPN and its detrimental impact on QoL in a population from eastern Iran. It reinforces the association between elevated systemic inflammatory markers and DPN. However, the nonsignificant multivariate regression model indicates that the determinants of QoL in this population are complex and not fully captured by inflammatory markers or traditional metabolic variables. Rather than identifying any single factor as an independent predictor, our findings suggest that QoL in DPN patients is multifactorial. Future longitudinal and interventional studies with larger sample sizes and more comprehensive measurement of potential confounders, including pain severity, depression, medication use, and socioeconomic factors, are needed to disentangle the causal pathways linking inflammation, metabolic factors, and QoL. Clinically, these findings advocate for a holistic, integrated management approach that addresses not only glycemic control but also psychosocial and socioeconomic determinants of quality of life in resource-limited settings.

STATEMENT OF ETHICS

In this study, ethical approval was obtained from the Ethics Committee of Zabol University of Medical Sciences (Approval Code: IR.ZBMU.REC.1402.063). Prior to participation, written informed consent was obtained from all individuals enrolled in the study.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

The data presented in this study are available on request from the corresponding author.

AI ASSISTANCE DISCLOSURE

The authors acknowledge the use of the DeepSeek AI assistant (DeepSeek Company) for English language polishing and formatting assistance during the preparation of this manuscript. All scientific content, data interpretation, and conclusions remain the sole responsibility of the authors.

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