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The effect of immunologic marker levels on the development of postherpetic neuralgia in diabetes mellitus patients with acute herpes zoster

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Ethical Approval
Ethical approval was obtained from the Necmettin Erbakan University Clinical Research Ethics Committee (Decision No. 2021/491; April 14, 2021) and the Turkish Ministry of Health (Approval No. E.66175679-514.04.03-559105; October 6, 2021). Written informed consent was obtained from all participants.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Neuropathic pain is a complex condition with an incompletely understood pathogenesis, and immunologic mechanisms are increasingly recognized as important contributors. This study aimed to evaluate the association between immunologic marker levels and the development of postherpetic neuralgia in patients with acute herpes zoster, with a particular focus on the impact of diabetes mellitus.
Methods: In this prospective observational study, 20 patients with acute herpes zoster and a Douleur Neuropathique 4 score of 4 or higher were enrolled. Patients were categorized into two groups: those with diabetes mellitus (Group I, n = 10) and those without diabetes mellitus (Group II, n = 10). Routine laboratory parameters, including hemogram, C-reactive protein, erythrocyte sedimentation rate, fasting blood glucose, and hemoglobin A1c, were recorded. Immunologic markers, including CD3+, CD4+, CD8+, FOXP3+ regulatory T cells, natural killer cell subsets (regulatory, defective, cytotoxic, CD56 bright, and CD56 dim), and NK CD57, were analyzed at baseline and at month 3.
Results: NK defective subset levels were lower in Group I than in Group II at baseline and at month 3 (P = 0.028 and P = 0.037, respectively). During follow-up, significant reductions in CD3+, CD4+, and CD8+ levels were observed in Group I (P = 0.013, P = 0.017, and P = 0.041, respectively), whereas significant decreases in NK defective and NK regulatory subsets were identified in Group II (P = 0.037 and P = 0.047, respectively). At the 3-month assessment, all patients met the study definition of postherpetic neuralgia.
Conclusion: Diabetes mellitus was associated with alterations in natural killer cell subpopulations, suggesting impaired innate immune function in patients with acute herpes zoster. However, within the limitations of this small cohort, diabetes mellitus did not appear to independently increase the risk of postherpetic neuralgia. Larger, well-designed studies are needed to clarify the predictive role of immunologic markers in chronic neuropathic pain outcomes.

Keywords: diabetes mellitus, herpes zoster, immune system, natural killer cells, postherpetic neuralgia

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Introduction

Postherpetic neuralgia is a debilitating clinical condition characterized by persistent pain in the dermatomal distribution affected by acute herpes zoster [1]. As a form of neuropathic pain, postherpetic neuralgia arises from damage to the somatosensory system and represents a substantial clinical burden, particularly in aging populations. The incidence and severity of postherpetic neuralgia are influenced by multiple risk factors, among which diabetes mellitus has been identified as an important clinical comorbidity [2].

Diabetes mellitus is associated with impaired immune function, including alterations in cell-mediated immunity, phagocytosis, and opsonization [3]. These immune dysfunctions may not only predispose individuals to infections such as herpes zoster but also influence the subsequent development of chronic pain conditions such as postherpetic neuralgia. However, the precise mechanisms linking immune dysregulation to neuropathic pain remain incompletely understood.

In recent decades, growing evidence from both experimental and clinical studies has highlighted the critical role of the immune system in the pathogenesis of neuropathic pain [4]. Increasing attention has therefore focused on immunologic markers and cytokine profiles that may modulate pain pathways and treatment responses [5]. Despite these advances, the relationship between specific immune-cell subsets and the development of postherpetic neuralgia, especially in patients with comorbid diabetes mellitus, remains insufficiently defined.

The present study aimed to investigate changes in immunologic marker levels in patients with acute herpes zoster and to compare these patterns between patients with and without diabetes mellitus. By evaluating the potential association between immune profiles and postherpetic neuralgia status, this study sought to provide additional insight into the neuroimmune mechanisms underlying persistent neuropathic pain.

Materials and methods

This prospective observational study was conducted between April 2022 and March 2023 in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Necmettin Erbakan University Clinical Research Ethics Committee (Decision No. 2021/491; April 14, 2021) and the Turkish Ministry of Health (Approval No. E.66175679-514.04.03-559105; October 6, 2021). Written informed consent was obtained from all participants before enrollment. Patients aged 18 to 80 years presenting with acute herpes zoster and a Douleur Neuropathique 4 score of 4 or higher were eligible. Patients with cancer, chemotherapy, pregnancy, immune deficiency, immunosuppressive drug use, severe comorbid disease, or drug allergy were excluded. Participants were categorized into two groups according to diabetes mellitus status: Group I included patients with diabetes mellitus, and Group II included patients without diabetes mellitus.

At baseline, demographic data, including age, sex, body mass index, affected dermatome, medication use, Numerical Rating Scale score, Sleep Interference Score, and Douleur Neuropathique 4 questionnaire score, were recorded. All patients received standard clinical management with pregabalin or gabapentin, with dosing individualized according to age, comorbidities, concomitant medications, and overall clinical status. No experimental interventions were introduced for the purpose of the study.

Routine laboratory parameters, including white blood cell count, C-reactive protein, erythrocyte sedimentation rate, fasting blood glucose, and hemoglobin A1c, were measured at baseline and at month 3. Peripheral blood samples were collected for immunologic analysis. Peripheral blood mononuclear cells were isolated from EDTA-anticoagulated blood. Surface staining was performed using monoclonal antibodies against cluster of differentiation 3, 4, 8, 16, 56, and 57 (Becton Dickinson, USA). Cells were analyzed using a BD FACSCanto II flow cytometer. The evaluated immune-cell subsets included CD3+, CD4+, CD8+, FOXP3+ regulatory T cells, NK defective cells, NK regulatory cells, NK cytotoxic cells, NK CD56 bright cells, NK CD56 dim cells, and NK CD57 cells.

The primary outcomes were changes in immunologic marker levels and the association between diabetes mellitus and postherpetic neuralgia status at month 3. Secondary outcomes included relationships between changes in clinical scores and routine laboratory parameters and postherpetic neuralgia status.

Statistical analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Chicago, IL, USA). Continuous variables were summarized as mean (SD), median, minimum, and maximum values, and categorical variables were presented as counts and percentages. Normality was assessed with the Kolmogorov-Smirnov test. Between-group comparisons were performed using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Within-group comparisons were performed using the Wilcoxon signed-rank test. A *P*-value of less than 0.05 was considered statistically significant.

Results

A total of 20 patients were included in the study, with 10 patients in Group I and 10 patients in Group II (Figure 1). The cohort consisted of 15 women (75.0%) and 5 men (25.0%). All patients in Group I had type 2 diabetes mellitus. There were no significant between-group differences in age, sex distribution, or body mass index (P = 0.305, P = 0.606, and P = 0.850, respectively) (Table 1).

Table 1. Baseline demographic characteristics of the patients

Variable	Group I (n = 10)	Group II (n = 10)	*P* value
Age, years	70.4 (6.6)	63.2 (18.3)	0.305
Female sex, n (%)	8 (80.0)	7 (70.0)	0.606
Body mass index, kg/m²	28.65 (2.92)	28.92 (6.08)	0.850

Data are presented as mean (SD) unless otherwise stated. BMI: body mass index, Group I: patients with diabetes mellitus, Group II: patients without diabetes mellitus. $P < 0.05$ was considered statistically significant.

As shown in Table 2, fasting blood glucose and hemoglobin A1c levels were higher in Group I than in Group II at baseline (P = 0.028 and P = 0.006, respectively) and at month 3 (P = 0.021 and P = 0.014, respectively). Other routine laboratory parameters were comparable between the groups at both time points. Within-group analyses showed no significant temporal changes in Group I, whereas Group II demonstrated significant reductions in C-reactive protein (P = 0.005) and erythrocyte sedimentation rate (P = 0.036).

Figure 1. Flow diagram of patient enrollment, group allocation, follow-up, and analysis

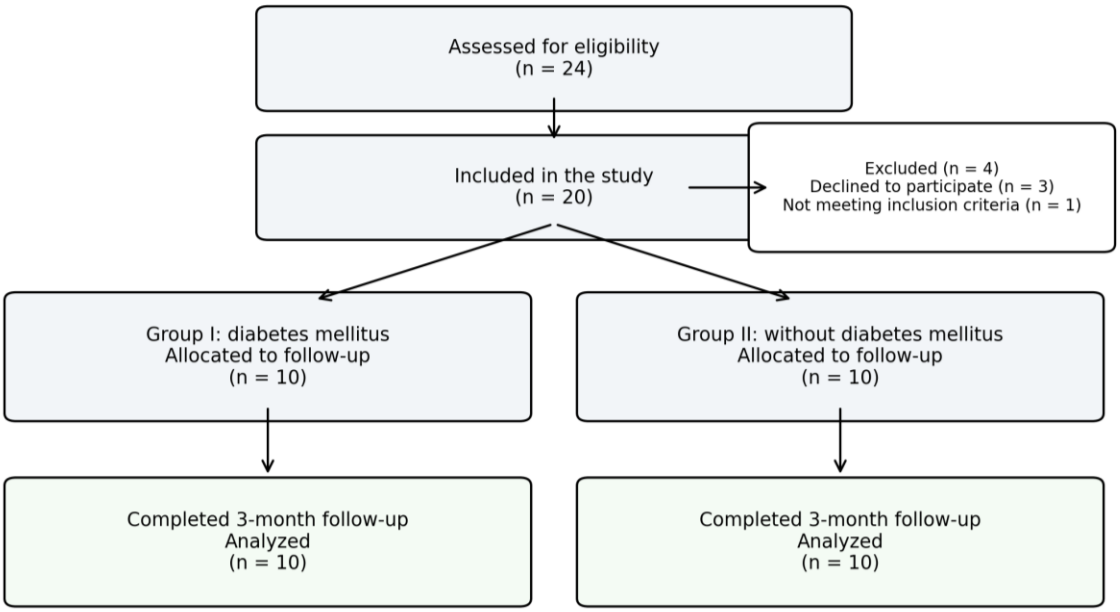


Table 2. Comparison of routine laboratory tests at baseline and month 3 between and within the groups

Variable	Time point	Group I (n = 10)	Group II (n = 10)	*P*-value
WBC, ×10³/µL	Baseline	7.88 (2.91)	8.01 (2.48)	0.734
	Month 3	7.51 (2.48)	6.70 (1.25)	0.520
	Within-group *P* value	0.646	0.093	
CRP, mg/dL	Baseline	12.38 (18.84)	7.05 (7.01)	0.970
	Month 3	10.63 (16.14)	3.45 (3.98)	0.850
	Within-group *P* value	0.386	0.005*	
ESR, mm/h	Baseline	16.30 (8.99)	15.40 (8.59)	0.733
	Month 3	14.80 (9.26)	8.60 (3.98)	0.052
	Within-group *P* value	0.683	0.036*	
FBG, mg/dL	Baseline	167.80 (77.81)	102.60 (20.70)	0.028*
	Month 3	162.42 (98.90)	101.30 (21.36)	0.021*
	Within-group *P* value	0.575	0.683	
HbA1c, %	Baseline	8.50 (2.48)	6.10 (0.59)	0.006*
	Month 3	7.85 (1.76)	6.08 (0.59)	0.014*
	Within-group *P* value	0.811	0.722	

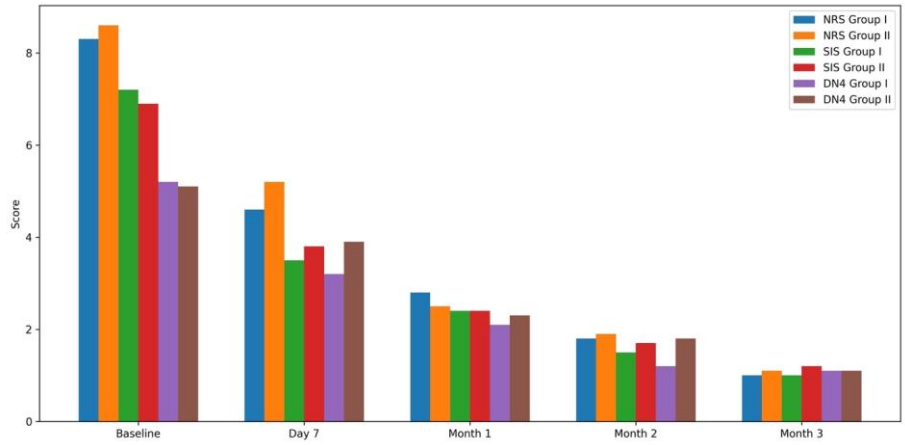
Data are presented as mean (SD). WBC: white blood cell count, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, FBG: fasting blood glucose, HbA1c: hemoglobin A1c. *$P < 0.05$ was considered statistically significant.

Table 3. Comparison of immunologic marker levels at baseline and month 3 between and within the groups

Variable	Time point	Group I (n = 10)	Group II (n = 10)	*P*-value
CD3+, %	Baseline	57.42 (11.34)	58.35 (11.06)	0.650
	Month 3	43.42 (9.65)	48.33 (17.75)	0.597
	Within-group *P* value	0.013*	0.059	
CD4+, %	Baseline	35.53 (7.16)	37.53 (10.75)	0.650
	Month 3	27.40 (8.57)	32.36 (14.58)	0.545
	Within-group *P* value	0.017*	0.074	
CD8+, %	Baseline	21.89 (8.36)	20.82 (8.67)	0.734
	Month 3	16.02 (2.86)	15.97 (6.45)	0.450
	Within-group *P* value	0.041*	0.059	
FOXP3+ (Treg), %	Baseline	7.84 (1.55)	6.84 (2.77)	0.723
	Month 3	7.84 (1.55)	7.25 (2.78)	0.705
	Within-group *P* value	0.074	0.386	
NK defective subset, %	Baseline	8.56 (9.24)	17.28 (11.42)	0.028*
	Month 3	3.49 (2.72)	7.53 (4.39)	0.037*
	Within-group *P* value	0.241	0.037*	
NK regulatory subset, %	Baseline	4.03 (2.93)	9.18 (7.21)	0.075
	Month 3	6.19 (7.28)	3.78 (2.63)	1.000
	Within-group *P* value	0.767	0.047*	
NK cytotoxic subset, %	Baseline	17.77 (12.37)	26.92 (15.07)	0.199
	Month 3	14.76 (10.10)	18.44 (11.84)	0.596
	Within-group *P* value	0.721	0.203	
NK CD57, %	Baseline	11.69 (7.69)	17.21 (12.01)	0.406
	Month 3	10.43 (7.46)	10.80 (5.67)	0.705
	Within-group *P* value	0.386	0.241	
NK CD56 bright, %	Baseline	2.71 (1.97)	3.63 (2.20)	0.427
	Month 3	3.65 (3.29)	3.23 (3.31)	0.705
	Within-group *P* value	0.445	0.441	
NK CD56 dim, %	Baseline	17.72 (12.40)	25.78 (11.22)	0.174
	Month 3	13.78 (9.55)	20.20 (15.79)	0.307
	Within-group *P* value	0.721	0.185	

Data are presented as mean (SD). FOXP3: forkhead box P3, Treg: regulatory T cell, NK: natural killer. *$P < 0.05$ was considered statistically significant.

Figure 2. Change in Numerical Rating Scale, Sleep Interference Score, and Douleur Neuropathique 4 scores during follow-up



DN4: Douleur Neuropathique 4, NRS: Numerical Rating Scale, SIS: Sleep Interference Score.

Immunologic assessment revealed significant differences in natural killer cell subsets between the groups (Table 3). The NK defective subset was lower in Group I than in Group II at baseline and at month 3 ($P = 0.028$ and $P = 0.037$, respectively). Over time, Group I showed significant declines in CD3+, CD4+, and CD8+ levels ($P = 0.013$, $P = 0.017$, and $P = 0.041$, respectively), whereas Group II showed significant reductions in NK defective and NK regulatory subsets ($P = 0.037$ and $P = 0.047$, respectively).

Pain-related outcomes did not differ significantly between the groups at any assessment point (Figure 2). For Numerical Rating Scale scores, between-group comparisons were not significant at baseline, day 7, month 1, month 2, or month 3 ($P = 0.614$, $P = 0.758$, $P = 0.531$, $P = 0.788$, and $P = 0.317$, respectively). Similarly, Sleep Interference Scores did not differ significantly between the groups at baseline, day 7, month 1, month 2, or month 3 (P = 0.810, $P = 0.759$, $P = 0.871$, $P = 0.675$, and $P = 0.453$, respectively). Douleur Neuropathique 4 questionnaire scores also showed no significant between-group differences at baseline, day 7, month 1, month 2, or month 3 ($P = 0.542$, $P = 0.197$, $P = 0.562$, $P = 0.066$, and $P = 0.317$, respectively). Both groups demonstrated progressive improvement in pain and symptom scores throughout follow-up. At the 3-month assessment, all patients met the study definition of postherpetic neuralgia.

Discussion

In this prospective observational study, patients with diabetes mellitus and acute herpes zoster exhibited lower natural killer defective subset levels than patients without diabetes mellitus, and immunologic markers changed dynamically during follow-up. However, all patients met the study definition of postherpetic neuralgia at month 3, and diabetes mellitus was not associated with a different postherpetic neuralgia outcome within this cohort.

Alterations in T-lymphocyte subsets have been inconsistently associated with postherpetic neuralgia in previous studies. In the present cohort, CD3+, CD4+, and CD8+ levels decreased over time in patients with diabetes mellitus, suggesting modulation of adaptive immune responses. Some studies have linked reduced T-cell counts to an increased risk of postherpetic neuralgia [6-8], whereas others have not confirmed this association [9]. Our findings are more consistent with the latter interpretation and may indicate that T-cell changes alone are insufficient to distinguish postherpetic neuralgia outcomes in a high-risk population.

Regulatory T cells are known to suppress neuroinflammation and may contribute to pain resolution [10]. In this study, FOXP3+ regulatory T-cell levels showed a modest, non-significant increase over time in both groups, while inflammatory markers declined more clearly in patients without diabetes mellitus. This pattern may reflect a more effective anti-inflammatory response in patients without diabetes mellitus. Nevertheless, the limited sample size requires cautious interpretation.

The findings also suggest differences in innate immune responses between the groups. Natural killer cell subsets were consistently lower in patients with diabetes mellitus, supporting the concept of diabetes-related impairment in innate immunity. In contrast, patients without diabetes mellitus showed more dynamic changes in NK-related subsets during follow-up. Previous studies have suggested a potentially protective role of natural killer cells in neuropathic pain conditions [11]. In this context, the attenuated NK-cell profile observed in patients with diabetes mellitus may reflect altered neuroimmune interactions after herpes zoster.

Routine inflammatory markers supported a similar pattern. C-reactive protein and erythrocyte sedimentation rate decreased significantly only in the group without diabetes mellitus, whereas patients with diabetes mellitus showed a less distinct inflammatory resolution profile. This observation is compatible with the recognized relevance of inflammatory markers in zoster-related outcomes and with clinical correlations reported in varicella-zoster infection [12, 13]. Because all patients received pregabalin or gabapentin as part of standard care, treatment-related immunomodulatory effects should also be considered when interpreting these laboratory changes [14].

An important contextual finding is that all patients in this cohort met the postherpetic neuralgia definition at month 3. This may be related to the selection criteria, because only patients with acute herpes zoster and clear neuropathic pain features were enrolled. Such a cohort likely represents a clinically high-risk subgroup in whom chronic pain mechanisms may already have been initiated during the acute phase. In addition, the small sample size and the absence of a comparator group without postherpetic neuralgia limited outcome variability.

This study has several limitations. The small sample size restricts generalizability and reduces the power to detect subtle between-group differences. The absence of a control group

without postherpetic neuralgia prevents direct comparison with patients who recover without chronic pain. Because all patients met the postherpetic neuralgia definition at month 3, subgroup analyses according to postherpetic neuralgia development were not possible. In addition, pregabalin or gabapentin treatment may have affected immune-cell dynamics, and cytokine profiling or functional immune assays were not performed.

In conclusion, diabetes mellitus may be associated with alterations in natural killer cell subpopulations in patients with acute herpes zoster, suggesting a potential impairment of innate immune responses. However, within the limitations of this small prospective cohort, diabetes mellitus was not identified as an independent determinant of postherpetic neuralgia status at month 3. Larger and methodologically broader studies are needed to clarify how immune dysregulation contributes to the pathogenesis of postherpetic neuralgia.

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