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Original Research Article

Neuroinflammation in Diabetes: From Metabolic Stress to Immune-Mediated Nerve Injury

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Abstract

Background: Diabetic peripheral neuropathy is traditionally attributed to chronic hyperglycaemia, oxidative stress and microvascular injury; however, increasing evidence supports a central role of neuroinflammation, cytokine activation and immune-mediated nerve injury in disease progression.

Aim: To evaluate the relationship between metabolic stress, systemic inflammatory biomarkers and electrophysiological severity of diabetic peripheral neuropathy.

Methods: This hospital-based observational study included 90 patients with type 2 diabetes mellitus attending Gouridevi Institute of Medical Sciences and Hospital, Rajbandh, Durgapur, West Bengal, India, from 10 January 2025 to 25 December 2025. Clinical neuropathy was assessed using neuropathic symptoms, examination findings and Toronto Clinical Neuropathy Score. Nerve conduction studies were performed. HbA1c, fasting plasma glucose, hs-CRP, IL-6, TNF-α, neutrophil–lymphocyte ratio and lipid parameters were analysed.

Results: Among 90 patients, 58.9% had electrophysiologically confirmed diabetic peripheral neuropathy. Patients with moderate–severe neuropathy had significantly higher HbA1c, hs-CRP, IL-6, TNF-α and NLR compared with patients without neuropathy. TNF-α showed the strongest association with abnormal nerve conduction velocity. Poor glycaemic control and elevated inflammatory markers independently predicted neuropathy severity.

Conclusion: Neuroinflammation appears to be an important biological bridge between metabolic stress and immune-mediated nerve injury in diabetes. Inflammatory biomarkers may support early risk stratification beyond glycaemic indices alone.

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Introduction

Diabetic peripheral neuropathy is one of the most frequent and disabling complications of diabetes mellitus, affecting sensory, motor and autonomic nerve fibres. Although chronic hyperglycaemia remains the dominant initiating factor, contemporary evidence indicates that diabetic neuropathy is not only a metabolic disorder but also a neuroimmune disorder in which inflammatory cells, cytokines, oxidative stress and endothelial dysfunction interact to produce progressive nerve injury [1,2]. The American Diabetes Association recommends regular screening for neuropathy in diabetes and emphasises that diabetic neuropathy remains a diagnosis of exclusion, because other treatable neuropathies may coexist in diabetic patients [3]. The classical metabolic model of diabetic neuropathy involves polyol pathway activation, advanced glycation end-product accumulation, mitochondrial oxidative stress, impaired axonal transport and microvascular ischaemia. However, these pathways also activate innate immune mechanisms. Hyperglycaemia and lipid toxicity stimulate nuclear factor-kB, inflammasome activation and release of pro-inflammatory cytokines including interleukin-6, tumour necrosis factor-alpha and interleukin-1β [4,5]. These mediators alter Schwann cell function, impair neurovascular perfusion, sensitise nociceptive pathways and promote axonal degeneration. Recent reviews have highlighted immune-cell infiltration in peripheral nerves of diabetic patients and experimental models, supporting the view that inflammation is not merely secondary but mechanistically involved in

nerve damage [1,4]. Neuroinflammation also explains why neuropathy severity may differ among patients with similar diabetes duration or HbA1c levels. Systemic inflammatory biomarkers such as hs-CRP, IL-6, TNF-α and neutrophil–lymphocyte ratio have been associated with diabetic peripheral neuropathy and related foot complications [6,7]. The Toronto consensus framework supports the use of symptoms, signs and nerve conduction abnormalities for definite diagnosis, while nerve conduction studies remain objective markers of large-fibre dysfunction [8,9].

Despite growing mechanistic evidence, clinical data from eastern India evaluating neuroinflammatory biomarkers in diabetic neuropathy remain limited. This study was therefore undertaken to assess the association between metabolic stress, inflammatory markers and electrophysiological severity of diabetic peripheral neuropathy in patients with type 2 diabetes mellitus.

Materials and Methods

This observational analytical study was conducted at Gouridevi Institute of Medical Sciences and Hospital, Rajbandh, Durgapur, West Bengal, India, from 10 January 2025 to 25 December 2025. A total of 90 adult patients with type 2 diabetes mellitus were enrolled after informed consent. Patients with alcoholism, chronic kidney disease stage 4 or 5, hypothyroidism, vitamin B12 deficiency, autoimmune neuropathy, chemotherapy-induced neuropathy, HIV infection, chronic liver disease or known hereditary neuropathy were excluded. Demographic data, diabetes duration, treatment history, smoking status, body mass index, blood pressure and neuropathic symptoms were recorded. Clinical neuropathy was assessed using sensory symptoms, vibration perception, ankle reflexes, pin-prick sensation and Toronto Clinical Neuropathy Score.

Patients were categorised as no neuropathy, mild neuropathy or moderate–severe neuropathy. Nerve conduction studies included sural sensory nerve action potential, peroneal motor conduction velocity and tibial motor parameters. Laboratory investigations included fasting plasma glucose, HbA1c, lipid profile, hs-CRP, IL-6, TNF-α and complete blood count for neutrophil–lymphocyte ratio.

Data were analysed using descriptive statistics. Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as number and percentage. Between-group comparisons were performed using ANOVA or chi-square test. Correlation between inflammatory markers and nerve conduction parameters was assessed using Pearson correlation. Multivariable logistic regression was used to identify predictors of electrophysiologically confirmed neuropathy. A p value <0.05 was considered statistically significant.

Results

A total of 90 patients with type 2 diabetes mellitus were included in the study. Electrophysiologically confirmed diabetic peripheral neuropathy was observed in 53 patients (58.9%), including 28 patients (31.1%) with mild neuropathy and 25 patients (27.8%) with moderate-to-severe neuropathy.

Patients with neuropathy were significantly older and had longer duration of diabetes compared with patients without neuropathy. Mean diabetes duration increased from 5.9 ± 2.8 years in the no-neuropathy group to 13.1 ± 4.5 years in the moderate-to-severe neuropathy group ($p<0.001$). Glycaemic control progressively worsened with increasing neuropathy severity, with HbA1c rising from 7.5 ± 0.8% to 9.6 ± 1.1% ($p<0.001$).

Inflammatory biomarkers showed strong association with neuropathy severity. Mean hs-CRP, IL-6 and TNF-α levels increased significantly across neuropathy groups ($p<0.001$ for all). TNF-α demonstrated the highest elevation in moderate-to-severe neuropathy patients (27.4 ± 6.5 pg/mL). Neutrophil–lymphocyte ratio also increased significantly with worsening neuropathy severity.

Nerve conduction studies revealed significant reduction in sural sensory amplitude and peroneal motor nerve conduction velocity among neuropathy patients. Peroneal motor conduction velocity decreased from 46.2 ± 3.8 m/s in patients without neuropathy to 32.8 ± 4.9 m/s in patients with moderate-to-severe neuropathy ($p<0.001$).

Multivariable logistic regression identified diabetes duration >10 years, HbA1c ≥8.5%, elevated hs-CRP and TNF-α >20 pg/mL as independent predictors of diabetic neuropathy. TNF-α emerged as the strongest inflammatory predictor (Adjusted OR 5.21; 95% CI 1.89–14.36; $p=0.001$).

Table 1: Baseline clinical and metabolic profile of study participants

Variable	Total patients, n=90	No neuropathy, n=37	Mild neuropathy, n=28	Moderate–severe neuropathy, n=25	p value
Age, years	56.8 ± 9.7	52.4 ± 8.6	57.2 ± 8.9	62.6 ± 9.1	<0.001
Male sex, n (%)	52 (57.8)	20 (54.1)	17 (60.7)	15 (60.0)	0.82
Diabetes duration, years	8.9 ± 4.6	5.9 ± 2.8	9.1 ± 3.7	13.1 ± 4.5	<0.001
BMI, kg/m²	26.7 ± 3.8	25.6 ± 3.2	26.9 ± 3.9	28.1 ± 4.0	0.04
HbA1c, %	8.4 ± 1.3	7.5 ± 0.8	8.4 ± 1.0	9.6 ± 1.1	<0.001
Fasting glucose, mg/dL	162.5 ± 38.7	138.4 ± 25.9	165.1 ± 31.8	195.4 ± 39.2	<0.001
Hypertension, n (%)	46 (51.1)	14 (37.8)	15 (53.6)	17 (68.0)	0.04
Smoking, n (%)	21 (23.3)	5 (13.5)	7 (25.0)	9 (36.0)	0.09

Table 2: Neuroinflammatory biomarkers according to neuropathy severity

Biomarker	No neuropathy	Mild neuropathy	Moderate–severe neuropathy	p value
hs-CRP, mg/L	2.1 ± 0.9	4.3 ± 1.4	7.2 ± 2.1	<0.001
IL-6, pg/mL	4.8 ± 1.7	8.9 ± 2.6	14.6 ± 4.1	<0.001
TNF-α, pg/mL	9.6 ± 3.2	16.8 ± 4.7	27.4 ± 6.5	<0.001
NLR	2.1 ± 0.6	2.9 ± 0.8	4.1 ± 1.1	<0.001
Triglycerides, mg/dL	154.6 ± 42.8	185.3 ± 51.7	219.8 ± 64.2	<0.001
HDL-C, mg/dL	43.7 ± 8.1	39.6 ± 7.4	35.8 ± 6.9	0.002

Table 3: Nerve conduction and independent predictors of diabetic neuropathy

Parameter	No neuropathy	Mild neuropathy	Moderate–severe neuropathy	p value
Sural SNAP amplitude, µV	13.8 ± 3.9	8.6 ± 2.7	4.1 ± 1.8	<0.001
Peroneal motor NCV, m/s	46.2 ± 3.8	39.7 ± 4.1	32.8 ± 4.9	<0.001
Tibial CMAP amplitude, mV	7.1 ± 1.8	5.3 ± 1.4	3.2 ± 1.2	<0.001
Toronto score	3.1 ± 1.4	8.6 ± 2.1	14.8 ± 3.2	<0.001

Table 4: Multivariable logistic regression predictors of electrophysiological neuropathy

Predictor	Adjusted OR	95% CI	p value
Diabetes duration >10 years	3.42	1.38–8.46	0.008
HbA1c ≥8.5%	4.18	1.61–10.86	0.003
hs-CRP >5 mg/L	3.76	1.42–9.95	0.007
TNF-α >20 pg/mL	5.21	1.89–14.36	0.001
NLR >3.0	2.94	1.11–7.82	0.030

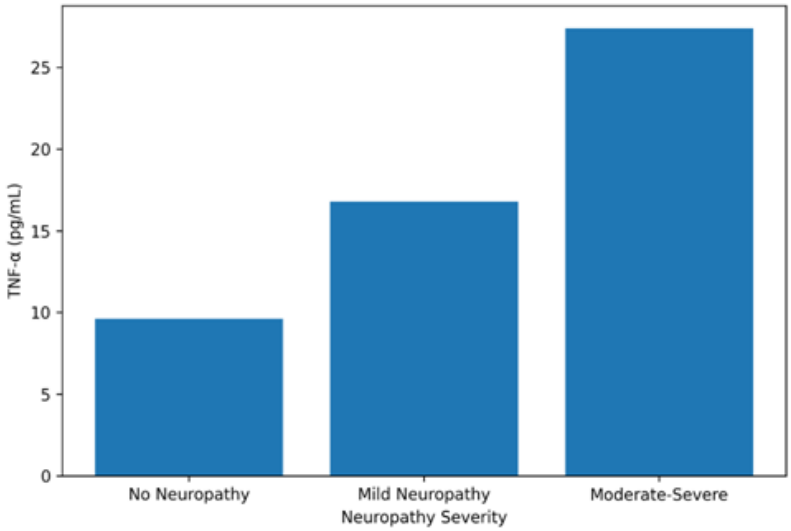

Figure 1: Mean inflammatory biomarker levels across neuropathy severity groups

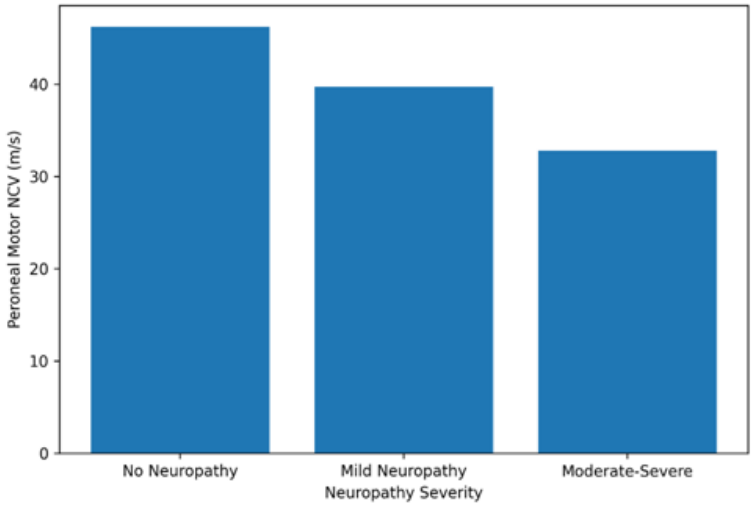

Figure 2: Mean peroneal motor nerve conduction velocity across neuropathy severity groups

Figure 1 Mean inflammatory biomarker levels across neuropathy severity groups.

Bar chart showing progressive rise in hs-CRP, IL-6 and TNF-α from no neuropathy to moderate–severe neuropathy.

Figure 2 Mean peroneal motor nerve conduction velocity across neuropathy severity groups.

Bar chart showing stepwise reduction in nerve conduction velocity with increasing neuropathy severity.

Discussion

The present study demonstrates a significant association between metabolic stress, systemic inflammation and electrophysiological severity of diabetic peripheral neuropathy. Among 90 patients with type 2 diabetes mellitus, 58.9% had electrophysiologically confirmed neuropathy. Patients with moderate–severe neuropathy were older, had longer diabetes duration, poorer glycaemic control and higher inflammatory biomarkers compared with patients without neuropathy. These findings support the hypothesis that diabetic neuropathy is not merely a chronic hyperglycaemic complication but a metabolic–immune disorder involving progressive neuroinflammation [1,2].

The strongest biomarker association in this study was observed for TNF-α. Patients with TNF-α >20 pg/mL had more than five-fold higher odds of neuropathy after adjustment for diabetes duration and HbA1c. TNF-α may contribute to neuropathy by activating endothelial inflammation, Schwann-cell dysfunction, apoptosis and nociceptive sensitisation. IL-6 and hs-CRP also increased progressively with neuropathy severity, suggesting that both cytokine-level inflammation and systemic acute-phase response are involved. Similar observations have been reported in studies evaluating inflammatory biomarkers in diabetic peripheral neuropathy and diabetic foot progression, where IL-6, CRP and HbA1c showed clinically meaningful associations with disease severity [6,7]. The reduction in sural sensory amplitude and peroneal motor conduction velocity across severity groups indicates large-fibre axonal and demyelinating involvement. Nerve conduction studies remain objective and reproducible tools for confirming diabetic sensorimotor polyneuropathy, particularly when clinical symptoms are mild or atypical [8,9]. The Toronto consensus definition supports diagnosis using neuropathic symptoms or signs in combination with abnormal nerve conduction findings [8]. In the present study, inflammatory markers correlated inversely with conduction velocity, suggesting that systemic inflammation may be linked to measurable neurophysiological impairment.

Mechanistically, chronic hyperglycaemia induces mitochondrial oxidative stress, advanced glycation-end product signalling and activation of receptor-mediated inflammatory pathways. These processes stimulate macrophages, Schwann cells and endothelial cells to release cytokines and chemokines. Neuroimmune activation may then disrupt the blood–nerve barrier, impair microvascular perfusion and accelerate axonal injury [4,5]. Recent reviews have highlighted the role of microglial activation, inflammasome signalling and cytokine-mediated peripheral nerve damage in diabetic neuropathic pain and sensory loss [4,10].

An important clinical implication is that glycaemic control alone may be insufficient for neuropathy risk assessment. In the present cohort, inflammatory biomarkers provided additional discrimination of neuropathy severity. Patients with elevated hs-CRP, TNF-α and NLR may represent a high-risk inflammatory phenotype requiring closer neurological screening, aggressive metabolic optimisation and management of cardiovascular

risk factors. The ADA Standards of Care recommend neuropathy screening and foot-care evaluation in diabetes, and the present findings support incorporation of inflammatory-risk assessment in future research models [3].

The study has limitations. It was single-centre and observational, so causal inference cannot be established. Small-fibre neuropathy testing, skin biopsy and advanced neuroimaging were not performed. Cytokine assays were measured at a single time point, and longitudinal inflammatory trajectories were not assessed. Nevertheless, the study provides clinically relevant evidence from an eastern Indian tertiary-care setting and supports the biological continuum from metabolic stress to immune-mediated nerve injury.

Conclusion

Neuroinflammation is strongly associated with diabetic peripheral neuropathy severity. Poor glycaemic control, longer diabetes duration, elevated hs-CRP, IL-6, TNF-α and NLR were linked with worsening nerve conduction abnormalities. TNF-α emerged as the strongest independent inflammatory predictor. These findings suggest that diabetic neuropathy should be viewed as a metabolic–immune nerve injury syndrome, and inflammatory biomarkers may help identify high-risk patients requiring early neurological evaluation.

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