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Original Research Article

Role of pro- and anti-inflammatory cytokines in diabetic neuropathy

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ABSTRACT

Background: Diabetic neuropathy (DN) is one of the most prevalent complications of type 2 diabetes mellitus, characterized by progressive peripheral nerve damage primarily resulting from chronic hyperglycaemia. Emerging evidence implicates inflammation as a key contributor to its pathogenesis. Pro-inflammatory cytokines such as IL-2, TNF-α and IL-6 promote neural injury, whereas anti-inflammatory cytokines like IL-10 and IL-4 may exert neuroprotective effects. This study aims to evaluate the serum levels of selected pro-inflammatory (IL-2, TNF-α, IL-6) and anti-inflammatory (IL-10, IL-4) cytokines in patients with diabetic neuropathy and to analyse their correlation with neuropathy severity.
Methods: A prospective, observational case control study was conducted involving 80 participants, comprising 40 diabetic neuropathy patients and 40 healthy controls at Thanjavur Medical College, Thanjavur, Tamil Nadu, India during the period of June 2025 to December 2025. Demographic characteristics, biochemical parameters and serum cytokine levels including interleukin (IL)-10, IL-4, IL-2, IL-6 and tumor necrosis factor-alpha (TNF-α) were analysed. Statistical analysis was performed using SPSS version 26.0.
Results: This study results showed that, IL-6 was significantly increased in diabetic neuropathy patients (median 8.35 (3.27–22.89) pg/mL) compared with healthy controls (2.39 (2.13–3.00) pg/ml) (p=0.007). IL-10 also demonstrated a significant change between groups (p=0.0003). No significant differences were observed for IL-4, IL-2 and TNF-α levels. Correlation analysis revealed that no significant association between HbA1c and cytokine levels. ROC curve analysis demonstrated that IL-10 exhibited the greatest diagnostic performance with an AUC of 0.882, followed by IL-6 with an AUC of 0.784.
Conclusions: The findings of the present analysis indicate that inflammatory dysregulation is associated with diabetes neuropathy patients. IL-6 and IL-10 emerged as the most significant potential cytokines and demonstrated promising diagnostic utility. These biomarkers may serve as valuable indicators of inflammation in diabetic patients and may contribute to the development of future diagnostic and therapeutic strategies. Further studies with larger sample sizes are warranted to validate these study findings.

Keywords: Cytokines, Diabetes, Neuropathy, Peripheral nerve

INTRODUCTION

Diabetes mellitus is a major global epidemic of the 21st century, with its incidence having increased by nearly 50% over the past decade. According to the World Health Organization (WHO), approximately 590 million adults live with diabetes worldwide. This number is projected to rise to about 642 million by 2040, representing nearly 8.8% of the global adult population.[1] Diabetes has systemic implications, affecting cardiovascular health,

kidney function, vision, peripheral circulation, oral health and immune response. These complications are expected to increase the global disease burden substantially in the coming decades.[2,3] It represents a serious chronic metabolic disorder associated with significant morbidity and mortality, primarily due to vascular and neurological complications. All forms of diabetes are characterized by chronic hyperglycaemia resulting from a relative or absolute deficiency in insulin secretion, impaired insulin action or both. This leads to selective insulin resistance and the development of diabetes-specific microvascular pathology, particularly in the retina, renal glomerulus and peripheral nerves.[4] More than half of individuals with diabetes eventually develop some form of neuropathy, with a lifetime risk of lower-extremity amputation estimated at up to 15% in certain populations.[5] Diabetic neuropathy encompasses a broad spectrum of disorders affecting both the somatic and autonomic divisions of the peripheral nervous system and, in some cases, the spinal cord and higher central nervous system. Pro-inflammatory cytokines such as IL-2, TNF-α and IL-6 promote neural injury, whereas anti-inflammatory cytokines like IL-10 and IL-4 may exert neuroprotective effects.6 This study aims to evaluate the serum levels of selected pro-inflammatory (IL-2, TNF-α, IL-6) and anti-inflammatory (IL-10, IL-4) cytokines in patients with diabetic neuropathy and to analyse their correlation with neuropathy severity.

METHODS

Study design

This was a prospective, observational case control study. Participants were recruited from the general medicine, non-communicable diseases (NCD) and Neurology Department at Thanjavur Medical College, Thanjavur, Tamil Nadu, India during the period of June 2025 to December 2025. Ethical approval was obtained from the Institutional Ethics Committee of Thanjavur Medical College before the commencement of the study.

Selection of the participants

Inclusion criteria comprised patients aged between 35 and 70 years, with a confirmed diagnosis of type 2 diabetes mellitus according to ADA criteria and evidence of diabetic neuropathy and having a duration of diabetes of at least five years. Patients were excluded if they had other causes of neuropathy such as alcoholism, toxin exposure or renal failure or if they presented with acute or chronic infections, autoimmune diseases, inflammatory disorders or were on anti-inflammatory or immunosuppressive therapy. A total of 40 patients diagnosed with type 2 diabetes mellitus (T2DM) and clinically confirmed diabetic neuropathy and 40 healthy people selected as controls were enrolled in this prospective study during the period of June 2025 to December 2025. The diagnosis of diabetic neuropathy was established through detailed clinical evaluation and electrophysiological confirmation using nerve conduction studies.

Clinical assessment and data collection

A comprehensive clinical evaluation was performed for all participants, including recording medical history, duration of diabetes, treatment details and neuropathic symptoms. Basic anthropological measurements such as age, gender, weight, height, waist circumference and Blood pressure were measured.

Blood sample collection and biochemical analysis:

For biochemical analysis, approximately 5 ml of venous blood was collected from each participant under aseptic conditions. The samples were allowed to clot at room temperature and serum was separated by centrifugation at 3000 rpm for 10 minutes. The serum aliquots were then stored at –80°C until further analysis. The biochemical analysis such as Glucose, HbA1c, Cholesterol, Triglycerides and HDL levels were determined using fully automatic biochemistry analyser (Erba EM-200).

Biomarker quantification

Biomarker analysis was performed using commercially available ELISA kits (ELK Biotechnology: IL-6 (Lot No. ELK1156), IL-2 (Lot No. ELK1149), IL-4 (Lot No. ELK1152), IL-10 (Lot No. ELK1142) and TNF-α (Lot No. ELK1190)) according to the manufacturer's instructions. The concentrations of the biomarkers were quantified using a Robonik ELISA reader.

Data analysis

The collected data were entered into Microsoft Excel and analysed using SPSS version 26.0. (SPSS Inc., Chicago, IL, USA). Results were expressed as mean±standard deviation (SD) or median (interquartile range, IQR) as appropriate. Sociodemographic data and biochemical parameters analysis between diabetic neuropathy patients and normal healthy controls were compared using the Independent Student's t-test. Cytokine levels (IL-10, IL-4, IL-2, IL-6 and TNF-α) were compared utilizing the Mann–Whitney U statistical test. Correlation between HbA1c and cytokine concentration was examined using Spearman's correlation study. Receiver operating characteristic (ROC) curve examination was determined to evaluate the diagnostic performance of various markers. The area under the curve (AUC), sensitivity and specificity were also calculated. P value less than 0.05 was considered statistically significant.

RESULTS

Demographic analysis investigated that diabetic neuropathy patients were significantly older than healthy controls (diabetic neuropathy 55.8±10.7, Control 44.8±6.8 years, p=0.003). Body weight and waist

circumference also differed significantly between both groups' neuropathy patients and control ($p<0.05$). No significant differences were observed in height, systolic blood pressure or diastolic blood pressure in both groups' neuropathy patients and control. The demographic characteristics of study participants showed in Table 1. Biochemical assessment revealed markedly elevated fasting glucose levels in diabetic neuropathy patients compared with healthy controls (Neuropathy patients 281.6±111.8, healthy controls 123.9±31.2 mg/dL, $p<0.001$) showed in Figure 1. HbA1c values were significantly higher in the diabetic Neuropathy group (diabetic population 6.91±2.48%, controls 4.97±1.21%, $p=0.004$), indicating poor glycemic control showed in Figure 2.

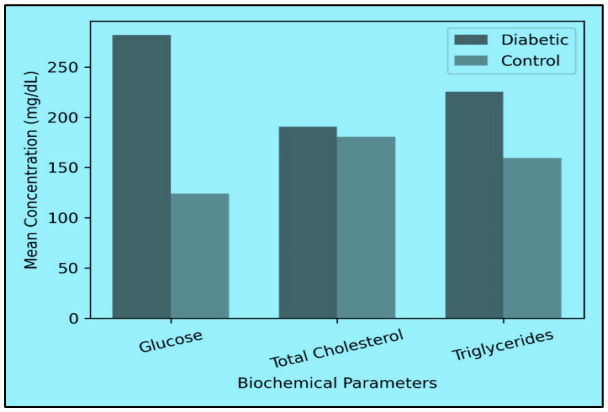

Figure 1: Comparison of mean serum glucose, total cholesterol and triglyceride concentrations between diabetic neuropathy patients' group and healthy controls group. The X-axis represents biochemical parameters and the Y-axis represents mean concentration expressed as mg/dl.

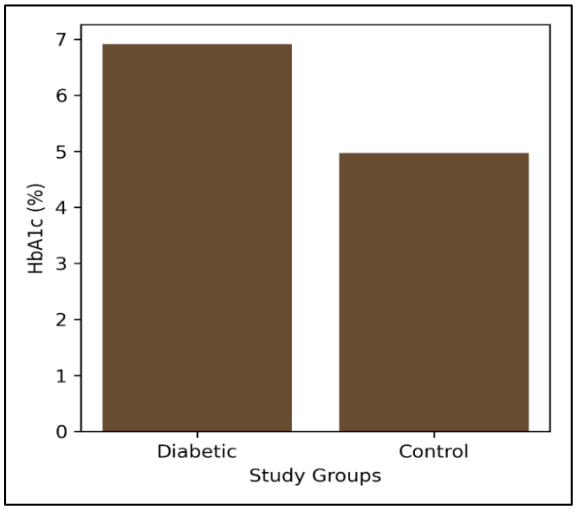

Figure 2: Comparison of mean glycated haemoglobin (HbA1c) levels between diabetic neuropathy patients' group and healthy controls group. The X-axis represents study groups and the Y-axis represents HbA1c (%).

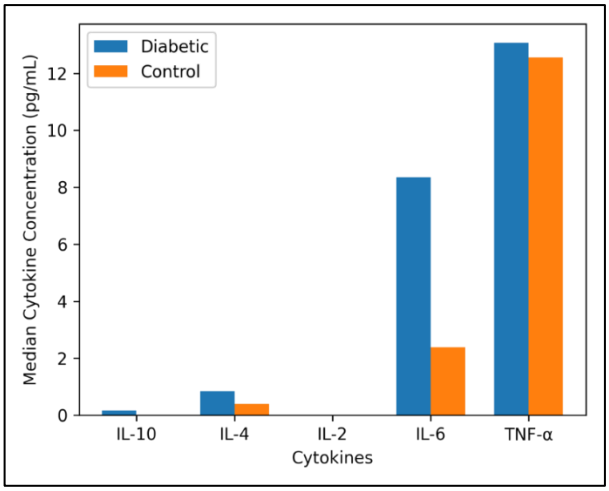

Figure 3: Comparison of serum Pro inflammatory and inflammatory cytokine levels between diabetic neuropathy patients and healthy controls. The X-axis represents the cytokines analysed (IL-10, IL-4, IL-2, IL-6 and TNF-α). The Y-axis represents median serum cytokine concentration expressed as picograms per millilitre (pg/ml).

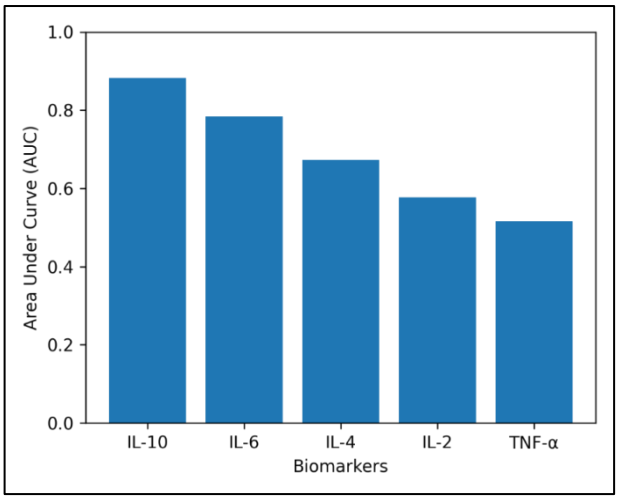

Figure 4: Receiver operating characteristic (ROC) analysis of cytokines for discrimination of diabetic patients from controls. IL-10 demonstrated the highest diagnostic performance (AUC=0.882), followed by IL-6 (AUC=0.784).

Triglycerides and VLDL concentrations were significantly increased in diabetic population (diabetic neuropathy group $p=0.006$ and control group $p=0.018$, respectively) showed in Figure 1. Although total cholesterol and LDL levels were higher in diabetic population, these differences did not reach statistical significance showed in Figure 1.

HDL concentrations were slightly lower in diabetic patients' group but were not significantly different from health controls group. The biochemical parameters showed in Table 2.

Comparison of inflammatory cytokines between diabetic neuropathy patients' group and healthy controls group revealed significant differences in IL-10 and IL-6 concentrations. Serum IL-10 levels were significantly higher in diabetic neuropathy group (median 0.17 pg/ml (IQR 0.03–4.07)) compared with controls group (0.02 pg/m (IlQR 0.01–0.02); p=0.0003).

Similarly, IL-6 levels were significantly elevated in diabetic neuropathy patients (8.35 pg/ml (IQR 3.27–22.89)) compared with controls (2.39 pg/ml (IQR 2.13–3.00); p=0.007). No significant differences were observed for IL-4 (p=0.101), IL-2 (p=0.471) or TNF-α (p=0.884). Cytokine profile in diabetic neuropathy patients and controls showed in Table 3 and Figure 3.

Spearman correlation evaluation demonstrated no statistically significant association between HbA1c and Pro inflammatory and inflammatory cytokine concentrations. However, IL-6 showed a weak positive correlation with HbA1c (r=0.265, p=0.075), suggesting a potential relationship between glycemic status and inflammatory activation. Correlation of HbA1c with cytokines (spearman correlation) showed in Table 4.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic utility of Pro inflammatory and inflammatory cytokines for differentiating diabetic neuropathy patients from healthy controls. IL-10 demonstrated the highest diagnostic accuracy with an AUC of 0.882 (95% CI: 0.77–0.99, p=0.0003), indicating excellent discriminatory performance. IL-6 also showed good diagnostic ability with an AUC of 0.784 (95% CI: 0.63–0.94, p=0.007). In meanwhile, IL-4, IL-2 and TNF-α exhibited limited diagnostic performance with AUC values below 0.70. These investigations suggest that IL-10 and IL-6 may serve as promising potential biomarkers for diabetes neuropathy-associated inflammatory alterations. The ROC Analysis of Cytokines for Discrimination of Diabetic Patients from Controls showed in figure 4 and Table 5.

Table 1: Demographic characteristics of study participants.

Variables	Diabetic patients (n=37) Mean±SD	Controls (n=10) Mean±SD	P value
Age (in years)	55.8±10.7	44.8±6.8	0.003
Height (cm)	159.6±9.4	161.3±8.4	0.624
Weight (kg)	59.7±13.8	75.2±8.9	0.001
Waist circumference (cm)	37.4±4.5	34.8±1.9	0.041
Systolic BP (mmHg)	127.1±17.4	119.0±7.5	0.112
Diastolic BP (mmHg)	80.2±7.8	78.5±4.8	0.486

Table 2: Biochemical parameters.

Parameters	Diabetic patients mean±SD	Controls mean±SD	P value
Glucose (mg/dl)	281.6±111.8	123.9±31.2	<0.001
HbA1c (%)	6.91±2.48	4.97±1.21	0.004
Total Cholesterol (mg/dl)	190.7±34.5	180.5±24.1	0.281
Triglycerides (mg/dl)	225.4±72.3	159.3±48.2	0.006
LDL (mg/dl)	103.2±28.8	96.5±18.8	0.374
HDL (mg/dl)	39.3±6.9	42.3±8.6	0.184
VLDL (mg/dl)	46.6±17.1	35.4±9.8	0.018

Table 3: Cytokine profile in diabetic neuropathy patients and controls.

Cytokine concentration (pg/ml)	Function of cytokines	Diabetic median (IQR)	Control median (IQR)	P value (Mann–Whitney U)
IL-10	Anti-inflammatory	0.17 (0.03–4.07)	0.02 (0.01–0.02)	0.0003
IL-4	Anti-inflammatory	0.85 (0.40–1.74)	0.39 (0.30–0.73)	0.101
IL-2	Pro-inflammatory	0.02 (0.02–0.70)	0.02 (0.01–0.02)	0.471
IL-6	Pro-inflammatory	8.35 (3.27–22.89)	2.39 (2.13–3.00)	0.007
TNF-α	Pro-inflammatory	13.08 (1.67–32.33)	12.55 (10.74–14.97)	0.884

Table 4: Correlation of HbA1c with cytokines (spearman correlation).

Cytokine	Spearman r	P value
IL-10	0.170	0.259
IL-4	0.164	0.276

Continued.

Cytokine	Spearman r	P value
IL-2	-0.010	0.947
IL-6	0.265	0.075
TNF-α	-0.225	0.132

Table 5: ROC Analysis of cytokines for discrimination of diabetic patients from controls.

Markers	AUC	95% CI	Sensitivity (%)	Specificity (%)	P value
IL-10	0.882	0.77–0.99	86.5	80.0	0.0003
IL-6	0.784	0.63–0.94	78.4	70.0	0.007
IL-4	0.673	0.50–0.85	67.6	60.0	0.101
IL-2	0.577	0.39–0.76	56.8	60.0	0.471
TNF-α	0.516	0.33–0.70	51.4	50.0	0.884

DISCUSSION

Diabetic peripheral neuropathy (DPN) is a debilitating complication of diabetes mellitus, characterized by progressive nerve damage driven by chronic hyperglycemia and systemic inflammation.[1,2,7] The pathophysiology of DPN is significantly influenced by pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α. These cytokines promote oxidative stress, vascular dysfunction and neuronal degeneration by activating important signalling pathways including NF-κB and MAPK.[8,9]

The present study examined the concentration of pro-inflammatory and anti-inflammatory cytokines in diabetic neuropathy group and compared to the healthy controls. The results showed a significant elevation in IL-6 levels and a significant change in IL-10 levels among diabetic patients. Furthermore, ROC analysis identified IL-10 (AUC=0.882) and IL-6 (AUC=0.784) as the most promising potential biomarkers for differentiating diabetic neuropathy patients from healthy controls. Diabetes mellitus is most recognized as a chronic low-grade inflammatory disorder characterized by persistent activation of immune and inflammatory pathways. Hyperglycaemia induced oxidative stress, advanced glycation end-product formation and activation of inflammatory signaling cascades, resulting in increased pro-inflammatory and anti-inflammatory cytokine production and tissue damage.[10] Chronic inflammation has been implicated in the development of insulin resistance, vascular dysfunction and diabetic complications.[11]

In the current study, serum IL-6 levels were significantly increased in diabetic neuropathy patients compared with healthy controls group showed in Table 3. IL-6 is a multifunctional pro-inflammatory cytokine that plays a major role in immune regulation, inflammation and metabolic dysfunction. Increased IL-6 levels have been observed in patients with diabetes neuropathy and are associated with insulin resistance, endothelial dysfunction and progression of diabetic complications.[12] The observed elevation in IL-6 helps to the hypothesis that inflammatory mechanisms contribute substantially to the pathogenesis of diabetes with other complications. IL-10 is a potent anti-inflammatory cytokine that suppresses inflammatory responses by inhibiting the production of pro-inflammatory mediators such as TNF-α, IL-1β and IL-6.[13]

Altered IL-10 levels observed in the present investigation may represent a compensatory mechanism aimed at limiting excessive inflammation incorporated with chronic hyperglycaemia. Prior analysis has been demonstrated that dysregulation of IL-10 contributes to impaired immune homeostasis and progression of inflammatory diseases.[13]

ROC analysis revealed that IL-10 demonstrated the greatest diagnostic accuracy among all cytokines studied, followed by IL-6. These observations suggest that inflammatory cytokines may serve as helpful biomarkers for identifying metabolic and immunological disturbances in diabetic neuropathy patients. The highest diagnostic performance of IL-10 indicates that anti-inflammatory regulatory pathways may be significantly affected during disease progression. Although IL-4, IL-2 and TNF-α did not show statistically significant differences in this analysis, alterations in these cytokines may still contribute to the overall inflammatory milieu associated with diabetes. The interaction between pro-inflammatory and anti-inflammatory cytokines is complex and imbalance in these pathways may influence the development of diabetic complications including neuropathy, nephropathy and cardiovascular disease.[14-17]

Overall, the findings of the present investigation highlight that the importance of Pro inflammatory and inflammatory cytokines in diabetes neuropathy.

Increased IL-6 and altered IL-10 levels indicate the presence of immune dysregulation and chronic inflammation in diabetic neuropathy patients. These cytokines may serve as potential biomarkers for disease monitoring and may provide insights into future therapeutic strategies targeting inflammatory pathways in diabetes.

Limitations

The present study was limited by its relatively small sample size and single-centre study. Only selected cytokines were evaluated in this study and potential confounding factors such as obesity, medication use and duration of diabetes were not fully controlled. Therefore, larger multicentre studies are needed to validate the findings.

CONCLUSION

The present study highlights a significant imbalance between pro- and anti-inflammatory cytokines in patients with diabetic neuropathy. Elevated levels of pro-inflammatory mediators such as TNF-α and IL-6, along with altered anti-inflammatory cytokines like IL-10 and IL-4, suggest that chronic low-grade inflammation plays a key role in the progression of neuropathic complications in diabetes. The strong positive correlations observed among IL-2, IL-4, IL-10 and TNF-α indicate coordinated immune activation and regulatory feedback within the cytokine network. These findings support the concept that cytokine dysregulation contributes to neuronal injury and may serve as potential biomarkers for disease severity and therapeutic targeting in diabetic neuropathy.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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