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RESEARCH ARTICLE

The role of cytokines in diabetic neuropathic pain

Diyabetik nöropatik ağrıda sitokinlerin rolü

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Abstract

Aim: To investigate the role of cytokines in painful diabetic neuropathy (PDN) (PDN) and compare findings with recent evidence.

Methods: Sixty patients with PDN and thirty healthy controls were studied. Serum TNF-α, TGF-β, IL-10, and IL-17 levels were measured by ELISA. Parametric and non-parametric tests were applied.

Results: TNF-α (6.35±1.64 vs 7.41±2.26 pg/mL; p<0.001) and TGF-β (513.6±358.6 vs 783.8±406.9 pg/mL; p=0.020) were significantly reduced in patients, while IL-10 and IL-17 showed no difference. Recent studies have consistently reported elevated TNF-α, IL-6, and IL-1β levels in painful phenotypes.

Conclusion: Our findings highlight an imbalance in cytokine regulation in PDN, with a central role for the TNF-α/TGF-β axis. Beyond pathogenesis, these cytokines may serve as potential biomarkers and therapeutic targets guiding future treatment strategies.

Keywords: Painful diabetic neuropathy; cytokines; TNF-α; TGF-β; IL-10; IL-17.

Özet

Amaç: Diyabetik nöropatiye bağlı ağrı (ADN) patogenezinde inflamatuvar sitokinlerin rolünü değerlendirmek ve güncel literatürle karşılaştırmaktır.

Yöntemler: ADN tanısı almış 60 hasta ile 30 sağlıklı kontrol incelendi. Serum TNF-α, TGF-β, IL-10 ve IL-17 düzeyleri ELISA ile ölçüldü. İstatistiksel analizde parametrik/non-parametrik testler kullanıldı.

Bulgular: TNF-α (6.35±1.64 vs 7.41±2.26 pg/mL; p<0,001) ve TGF-β (513.6±358.6 vs 783.8±406.9 pg/mL; p=0,020) düzeyleri hasta grubunda anlamlı olarak düşüktü. IL-10 ve IL-17'de fark saptanmadı. Güncel çalışmalar ise TNF-α, IL-6 ve IL-1β artışını özellikle ağrılı fenotipte bildirmektedir.

Sonuç: Bulgularımız, ADN'de sitokin dengesinin bozulduğunu ve özellikle TNF-α/TGF-β ekseninin merkezi rol oynadığını göstermektedir. Bu sitokinler yalnızca patogenezde değil, aynı zamanda yeni biyobelirteçler ve tedavi stratejileri için de yol gösterici olabilir.

Anahtar Kelimeler: Diyabetik nöropatiye bağlı ağrı; sitokinler; TNF-α; TGF-β; IL-10; IL-17.

INTRODUCTION

Diabetic neuropathy (DN) is among the most common long-term complications of diabetes mellitus and is a major clinical problem owing to its heterogeneous manifestations and impact on daily functioning (1). The painful form of DN is particularly debilitating, occurring in approximately 15–30% of cases and frequently associated with sleep disturbances, mood disorders, and increased healthcare utilization (2). These consequences emphasize the importance of clarifying the biological mechanisms that drive the onset and progression of PDN.

In recent years, a growing body of evidence has underscored the role of inflammation and immune imbalance in the pathogenesis of DN (3). Dysregulation of pro-inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), together with impaired activity of anti-inflammatory cytokines like interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), appears to promote axonal damage and enhance nociceptive sensitivity (4). Prospective cohort studies have further demonstrated that elevated TNF-α levels and adhesion molecules can predict neuropathy development years in advance, supporting their role as early biomarkers (5).

At the molecular level, recent findings suggest that NF-

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κB signaling links hyperglycemia-induced metabolic stress to sustained neuroinflammatory responses (6). In parallel, activation of the NLRP3 inflammasome has been implicated in the amplification of neuropathic pain, offering mechanistic insight into the interplay between metabolic dysregulation and immune activation (7).

Emerging studies also highlight the importance of neuronal ion channel dysfunction in PDN. In particular, maladaptive changes in TRPV1, TRPA1, and NaV1.7 channels are proposed to underlie abnormal pain perception and hyperalgesia (8). Furthermore, lifestyle-related factors, such as diet and physical activity, may interact with immune signaling and exacerbate neuroinflammatory cascades, pointing toward potential modifiable contributors (9).

Taken together, these findings support the view that PDN is not merely a metabolic complication but a multifactorial disorder shaped by neuroimmune interactions. Clarifying how inflammatory mediators, signaling cascades, and ion channel alterations converge may provide new therapeutic avenues and inform precision strategies for prevention and treatment (10).

METHODS

This cross-sectional observational study recruited sixty patients with a confirmed diagnosis of painful diabetic neuropathy (PDN) and thirty age- and sex-matched healthy controls. Demographic variables, including age, sex, and clinical history, were recorded for all participants to ensure comparability between groups (10). The mean duration of diabetes in the PDN cohort was approximately 8.5 years, indicating a substantial chronic disease burden (4).

Peripheral venous blood samples were collected from all subjects under standardized conditions, and serum levels of tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), interleukin-10 (IL-10), and interleukin-17 (IL-17) were quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit, according to the manufacturer's instructions (1).

Statistical analyses were performed using parametric (Student's t-test) and non-parametric methods (Mann–Whitney U test), contingent upon the distribution of the data as determined by the Kolmogorov–Smirnov test. Categorical variables were compared using the chi-square test. A two-tailed p-value <0.05 denoted statistical significance (7).Ethical approval for the study protocol was obtained from the institutional review board, and informed consent was secured from all participants prior to enrollment, in accordance with the Declaration of Helsinki (2).

RESULTS

The clinical and demographic characteristics of the 60 patients with PDN and the 30 healthy controls are presented in Table 1. No significant differences in age or gender distribution were found between the groups (p>0.05). The mean duration of diabetes in the PDN group was 8.5±4.2 years, indicating a substantial disease burden.

The comparison of cytokine levels is summarized in Table 2. TNF-α levels were significantly lower in the patient group (6.35±1.64 pg/mL) compared with the control group (7.41±2.26 pg/mL) (p<0.001). TGF-β levels were also significantly lower in the patient group (513.62±358.63 pg/mL) than in the control group (783.84±406.98 pg/mL) (p=0.02). No significant differences were observed for IL-10 (4.90±18.99 pg/mL in patients vs 3.87±14.42 pg/mL in controls; p=0.729) or IL-17 (1.98±0.49 pg/mL in patients vs 2.05±0.76 pg/mL in controls; p=0.871).

In summary, TNF-α and TGF-β levels were significantly reduced in the patient group, while IL-10 and IL-17 were similar. These findings suggest a potential imbalance in cytokine regulation in PDN, with a specific focus on the TNF-α/TGF-β axis.

Table 1. Clinical and demographic characteristics of the study groups

Characteristics	Control (n=30)	Painful DN (n=60)
Age (years)	52±8	54±9
Gender (F/M)	16/14	32/28
Disease duration (years)	-	8.5±4.2

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Table 2.	Comparison of cytokine levels between groups		
Cytokine	Control (n=30)	Painful DN	P
TNF-α (pg/mL)	7.41±2.26	6.35±1.64	<0.001
TGF-β (pg/mL)	783.84±406.98	513.62±358.63	0.020
IL-10 (pg/mL)	3.87±14.42	4.90±18.99	0.729
IL-17 (pg/mL)	2.05±0.76	1.98±0.49	0.871

Note: Data are presented as mean ± SD (standard deviation). DN: Diabetic neuropathy; PDN: Painful diabetic neuropathy.

DISCUSSION

The present investigation revealed significantly reduced serum concentrations of TNF-α and TGF-β in patients with painful diabetic neuropathy (PDN) compared to healthy controls, whereas no statistically meaningful differences were observed in IL-10 and IL-17 levels. These findings partially diverge from the prevailing narrative in the literature, wherein elevated proinflammatory cytokines are frequently reported as the immunological signature of PDN (11). Such discrepancies may plausibly be attributed to heterogeneity in study populations, variations in glycemic control, disease chronicity, and concomitant therapeutic regimens (10).

Emerging mechanistic data strongly suggest that chronic hyperglycemia and lipotoxicity activate NF-κB–mediated transcriptional cascades, thereby augmenting the assembly of the NLRP3 inflammasome and fueling a self-perpetuating cycle of neuroinflammation (7). The concomitant activation of microglial cells within the dorsal horn further potentiates central sensitization, thereby magnifying nociceptive input (6). The observation of reduced TGF-β levels in our cohort may be particularly salient, as this cytokine is widely recognized for its dual anti-inflammatory and neuroprotective functions; its depletion thus implies a relative failure of compensatory mechanisms (2).

Although IL-17 did not differ substantially between groups in this study, mounting evidence suggests that it functions as a pro-nociceptive mediator by facilitating cross-talk between T helper 17 (Th17) cells and glial elements (8). Consequently, a predominance of proinflammatory over anti-inflammatory signaling may underlie the chronicity of pain in diabetic neuropathy (3).

Our findings resonate with prior longitudinal and experimental reports emphasizing that cytokine profiles not only delineate pathogenic pathways but may also serve as biomarkers for patient stratification (5). Moreover, they underscore the therapeutic promise of interventions aimed at restoring immunological equilibrium, particularly those targeting the TNF-α/TGF-β axis. Adjunctive strategies, including optimization of glycemic control, dietary modulation, and lifestyle modification, may further attenuate inflammatory load and restore homeostasis (9).

Limitations

This study has several limitations. First, the sample size was relatively small, which may restrict generalizability. Second, the cross-sectional design does not allow causal inference between cytokine levels and PDN. Finally, unmeasured factors—such as medication use or metabolic control—may have influenced cytokine profiles. Prospective, adequately powered studies with standardized phenotyping are warranted.

CONCLUSION

In conclusion, these findings underscore the involvement of cytokine disequilibrium in the pathogenesis of PDN. The reduction in TNF-α and TGF-β indicates disruption of both pro-inflammatory and anti-inflammatory mechanisms, potentially contributing to persistent nociception (7). Translationally, profiling these cytokines may assist early identification of patients at risk, enable biomarker-guided stratification, and inform the selection or development of targeted immunomodulatory therapies—particularly those modulating the TNF-α/TGF-β axis. Implementing such approaches alongside optimization of metabolic control could improve long-term outcomes and quality of life.

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Ethical Approval: Approved by the Institutional Ethics Committee; decision number 13.7.2017/1; written informed consent was obtained from all participants (in accordance with the Declaration of Helsinki).

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